CLINICAL AND PHYSIOLOGICAL RESPONSES TO GRADED VENESECTION IN THE MANAGEMENT OF ERYTHROCYTOSIS

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Contents

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Declaration

I, Richard Ian Raine, declare that the work on which this dissertation is based is original and my own work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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Chapter 1

Introduction

Erythrocytosis is a condition in which the haemoglobin concentration or red cell mass is increased to abnormally high levels. This may be primary, due to haematologic malignancies, or secondary to phenomena which are either physiologically appropriate, such as long-standing hypoxia, or physiologically inappropriate, resulting from conditions with increased erythropoietic drive. Erythrocytosis results in hyperviscosity, which may cause dysfunction or infarction in cerebrovascular, coronary arterial or peripheral vascular circulations.

Therapeutic venesection plays an important role in the management of patients with an expanded red cell mass. The beneficial effect of reduction in viscosity on microvascular perfusion is, however, offset to a degree by the concurrent decrease in oxygen carrying capacity per unit volume occurring after phlebotomy. Thus, overall tissue oxygenation will improve with more efficient perfusion, provided that the perfusing blood contains sufficient oxygen to meet metabolic requirements. Accordingly, the physician is confronted with the question of which packed cell volume (PCV) will best serve the patient's needs in terms of this specific end-point. There is some

evidence to suggest that the PCV should be less than 0.50 $L \cdot L^{-1}$ in erythrocytosis secondary to hypoxic lung disease[1], and that improvement in pulmonary haemodynamics, oxygen transport and cerebral blood flow will follow venesection to this level[1-4]. Despite a consensus derived from several publications that return of PCV into the normal range protects patients from morbidity and mortality, debate continues about the extent of venesection necessary for optimal tissue oxygen delivery.

The aim of this study was to determine the level of packed cell volume for optimal function in a group of patients with erythrocytosis by performing a variety of investigations at presentation and during progressive venesection to PCV of 0.40 $L \cdot L^{-1}$.

This introductory literature review addresses the background to the study by looking at the physiology of erythropoiesis; the classification and diagnosis of erythrocytosis; the morbidity associated with erythrocytosis; and the management of erythrocytosis.

1.1 Control of red cell production

Efficient functioning of the body depends upon an adequate supply of oxygen to the tissues. This in turn depends upon the ability of blood to carry oxygen and the flow of blood through the tissues. Haemoglobin is essential for the carriage of oxygen due to its unique reversible binding characteristics[5]. The

amount of haemoglobin is under careful physiological control to maintain an optimal concentration for oxygen carriage. There are two conflicting forces which require to be balanced. These are haemoglobin concentration and erythrocyte mass which are opposed by the rheological disturbances resulting from increased viscosity caused by increases in haemoglobin concentration or erythrocyte mass. In most individuals the red cell mass is efficiently modulated so that effective function can continue.

The initial response by the body to changes in oxygen delivery involves cardiovascular and respiratory adjustments, these include increases in cardiac output and minute ventilation[6]. Conformational changes in the haemoglobin molecule resulting in local changes in haemoglobin affinity to increase or decrease the amount of oxygen bound to haemoglobin occur continuously[5]. If the disturbance lasts beyond a few minutes, increased glycolytic activity results in increases in the levels of the intermediate metabolite, 2,3-diphosphoglycerate. Increased levels of this compound cause decreased affinity of haemoglobin for oxygen and facilitates release of oxygen in the tissues[7,8].

More prolonged homeostasis of oxygen delivery (after 1 to 2 hours) is by feedback control of red cell production. Oxygen deprivation of tissues results in release or activation of erythropoietin by the kidneys.

Erythropoietin is a glycoprotein produced predominantly by the kidneys[9]. A heme-containing protein senses oxygen lack and causes synthesis and release of erythropoietin[10]. Erythropoietin stimulates the differentiation and maturation of progenitor cells committed to the erythroid lineage (BFU-E)[11]. These then mature and proliferate to produce mature erythroid forms. It appears that there is an erythropoietin-dependent negative feedback system to regulate red cell production. The normal control of erythropoiesis is summarised in **figure 1.1**[12].

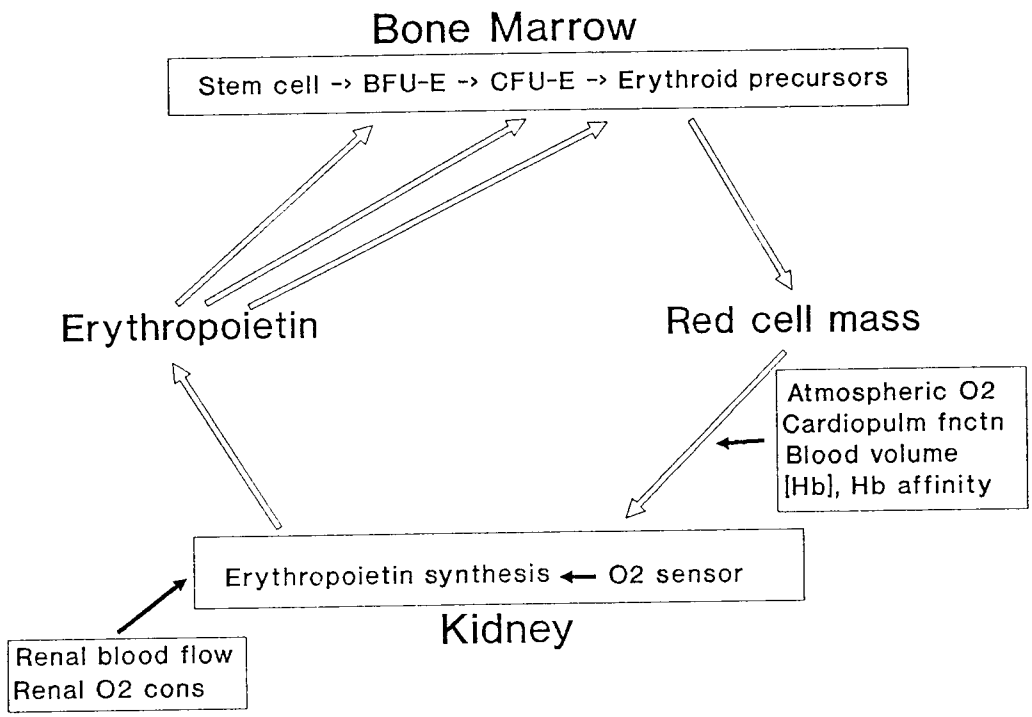


Figure 1.1: Control of erythropoiesis

The most important consequence of increased PCV is increased whole-blood viscosity and the resulting complications. The

management of erythrocytosis depends upon the aetiology, the clinical manifestations, and complications.

Erythrocytosis may be absolute or relative[13]. The distinction between relative and absolute erythrocytosis can only be definitively made on measurement of red cell mass and plasma volume by radio-isotopic techniques[14,15]. Relative erythrocytosis is characterised by normal red cell mass and contracted plasma volume. Common causes of this syndrome (also termed "spurious erythrocytosis", "stress erythrocytosis" or "Gaisböck's syndrome") include smoking, heavy use of alcohol and diuretic use[14]. Since the aetiology and management of this condition differ to other forms of erythrocytosis, this topic will not be considered further.

1.2 Classification and diagnosis of erythrocytosis

Absolute or true erythrocytosis is characterised by an expanded red cell mass. The origin of this expansion may be primary, because of malignant proliferation of haematopoietic cell lines, or secondary, because of uncontrolled production of erythropoietin or erythropoietin-like substance[13].

1.2.1 Primary erythrocytosis

Primary erythrocytosis is usually due to polycythaemia vera (PV). PV is a rare haematologic malignancy characterised by excessive proliferation of erythroid, myeloid and megakaryocytic

elements of the bone marrow[16]. The most usual presentation is with proliferation of myeloid constituents, with erythrocytosis or thrombocytosis. This eventually, in most cases, terminates in myelofibrosis, myelodysplasia or blastic transformation[17-20]. The diagnosis of PV is made according to criteria laid down by the Polycythemia Vera Study Group. These criteria are to be found in **table 1.1**[13].

Table 1.1: Criteria for diagnosis of polycythaemia vera

Categories	
A1 Red cell mass Male: ≥ 36 mL/kg Female: ≥ 32 mL/kg	B1 Thrombocytosis Platelets > 400 x 10^9/L
A2 S_aO_2 ≥ 92%	B2 WCC > 12 x 10^9/L (No fever/ infection)
A3 Splenomegaly	B3 LAP > 100 (No fever/ infection) Serum B_{12} > 900 pg/mL
Diagnosis acceptable with: A1 + A2 + A3 or: A1 + A2 + (any two from category B)	

1.2.2 Secordary erythrocytosis

Secondary erythrocytosis is an absolute increase in red cell mass with normal or elevated plasma volume. This is usually due to continued erythropoietin stimulation of red cell production[21].

Occasional reports of erythrocytosis secondary to other factors, such as azidothymidine[22], are found, but these are uncommon.

The causes of secondary erythrocytosis can be divided into those with increased erythropoietin drive secondary to diminished tissue oxygen supply ("physiologically appropriate"), and those in which autonomous over-production of erythropoietin occur ("physiologically inappropriate"). **Table 1.2** lists most of the described causes of secondary erythrocytosis.

Table 1.2: Causes of secondary erythrocytosis

(Modified from Berlin[13])

1. "Physiologically appropriate" (decreased tissue oxygen supply)
    a. High altitude
    b. Hypoxic lung disease
    c. Congenital heart disease
    d. Sleep apnoea syndromes
    e. Obesity-hypoventilation syndrome
    f. Haemoglobinopathy
    g. Smoking
    h. Chronic liver disease[23,24]
2. "Physiogically inappropriate"
    a. Tumours
        i. Renal carcinoma[25]
        ii. Cerebellar haemangioblastoma[26]
        iii. Hepatoma
        iv. Uterine fibroids
        v. Ovarian carcinoma
    b. Renal
        i. Cysts[27]
        ii. Hydronephrosis
        iii. Bartter's syndrome
        iv. Transplantation[28]
    c. Miscellaneous
        i. Zidovudine therapy in AIDS

Secondary erythrocytosis due to diminished tissue oxygen supply is the most common cause of true erythrocytosis. Decreased tissue oxygen supply may occur as a result of high altitude (decreased ambient oxygen tension)[29,30]; lung disease (ventilation-perfusion mismatching, diffusion gradient or hypoventilation)[31,32]; or congenital heart disease and chronic liver disease (right-to-left shunting)[23,24,33-35]. These conditions result in a chronic reduction in arterial oxygen saturation (S_aO_2) and sustained erythropoietin release. Occult causes of erythrocytosis include the obesity-hypoventilation and sleep apnoea syndromes, which may present with normal daytime S_aO_2, but marked falls in S_aO_2 during sleep[36,37].

Smoking causes an elevation in carboxyhaemoglobin (COHb), effectively reducing the amount of haemoglobin available for oxygen transport. COHb also causes a conformational change in haemoglobin structure, resulting in higher affinity of the haemoglobin molecule for oxygen[38,39].

This mechanism of left-shifting of the haemoglobin-oxygen dissociation curve is responsible for the tissue hypoxia and erythrocytosis seen in the haemoglobinopathies, many of which result in haemoglobin molecules with high affinity for oxygen and consequent tissue hypoxia[40].

There is no doubt that the erythrocytosis seen in hypoxic lung disease and cyanotic congenital heart disease is often a physiological overshoot. The correlation between arterial oxygen saturation levels and red cell mass or 2,3-diphosphoglycerate

levels is poor[41]. Some patients with secondary erythrocytosis can maintain a stable state with few symptoms and apparent side effects from erythrocytosis ("compensated"). A large number, however, are "decompensated" and PCV tends to rise with failure of negative feedback on erythropoiesis. These patients develop significant symptoms and problems from the elevated PCV and represent adaptive failure[34,35].

Other causes of secondary erythrocytosis are uncommon and many mechanisms have been described, including tumour production of erythropoietin, reduced erythropoietin catabolism, regional renal or hepatic ischaemia and the production of erythropoietin-like substances[12,21,22,26,42-44].

The cause of erythrocytosis can be established by following the algorithm portrayed in **figure 1.2**[13,16], which describes the diagnostic steps to be taken during investigation. The diagnosis of erythrocytosis secondary to smoking is often made once all other causes have been excluded because measurement of COHb levels, particularly in an in-patient setting may be misleading.

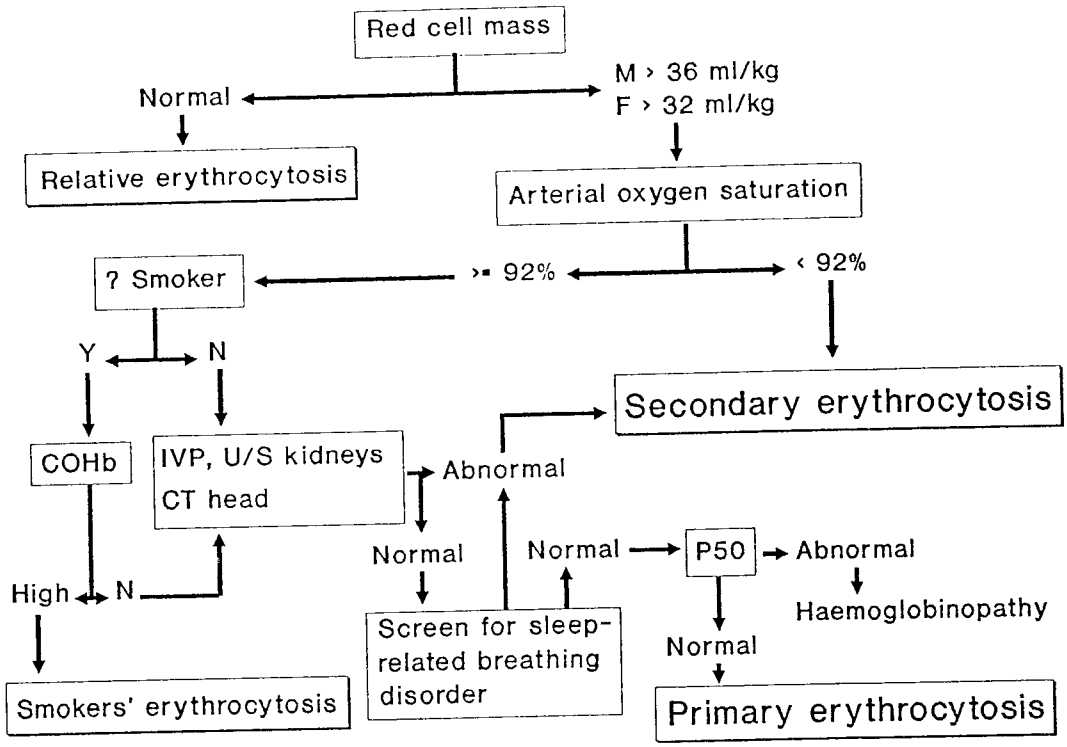


Figure 1.2: Algorithm for evaluation of elevated PCV

1.3 Complications of erythrocytosis

Erythrocytosis is associated with a number of complications, most due to decreased blood flow or stasis as a result of increased whole-blood viscosity. Increases in pulmonary and systemic vascular resistance, left and right heart failure, vascular occlusive events (arterial occlusion, deep venous thrombosis, and cerebral vascular accidents), and decreased cerebral blood flow resulting in poor concentration, headaches and impaired performance are commonly found.

1.3.1 Changes in haemodynamic variables

The effects of erythrocytosis on haemodynamic variables have been studied in a number of patients with erythrocytosis secondary to hypoxic lung disease and cyanotic congenital heart disease. In these patients it is difficult to divorce the effects of hypoxic pulmonary vasoconstriction and the inherent lung disease from the effects due to increased PCV and viscosity. Several of these studies[2-4,45-47], summarised in **table 1.3**, have repeated measurements of haemodynamic variables after therapeutic venesection. Changes in haemodynamics demonstrated under these conditions are thus likely to be due to the reduction in PCV and not the primary disease process alone.

Studies involving patients with hypoxic lung disease have shown that reduction in PCV by venesection reduces pulmonary artery pressures at rest and during exercise, as well as reducing pulmonary and systemic vascular resistance. In particular, Weisse et al[2] showed that reducing PCV from 0.62 to 0.50 $L \cdot L^{-1}$ reduced resting mean pulmonary artery pressure from 46 to 38 mm Hg. The pulmonary vascular resistance fell from 803 to 690 $dyne \cdot sec \cdot cm^{-5}$. Cardiac index was unaffected. There was no further fall in pulmonary artery pressure or pulmonary vascular resistance when the PCV was lowered to 0.44 $L \cdot L^{-1}$. The conclusion from this was that venesection to levels of lower than 0.50 $L \cdot L^{-1}$ was not beneficial in terms of haemodynamic improvement.

Segel and Bishop[3] showed that reducing PCV from 0.60 to 0.44 $L \cdot L^{-1}$ in 15 patients with hypoxic lung disease resulted in small falls in pulmonary artery pressure and pulmonary vascular resistance, while cardiac index did not change. Similar trends with reduced pulmonary vascular resistance and pulmonary artery pressures after venesection are evident in the other studies. Although there is a degree of variability in the results, there is an overall trend for pulmonary and systemic vascular resistance at rest and on exercise to fall following venesection. This suggests that at least part of the increased vascular resistance is due to erythrocytosis.

Chetty et al[48] studied 15 patients with hypoxia due to chronic obstructive pulmonary disease before and after venesection from mean PCV 0.60 $L \cdot L^{-1}$ to 0.51 $L \cdot L^{-1}$. Exercise duration increased by 50% and maximum oxygen uptake by 25% with no significant changes in maximum exercise heart rate or minute ventilation. They did not measure haemodynamic variables directly but interpreted the improved exercise performance to mean increased cardiac output during maximum exercise.

Similar, but small, improvements in haemodynamics at rest and on exercise accompanied reduction in PCV by venesection in PV[47]. Oldershaw and Sutton[33] studied 6 children with cyanotic congenital heart disease and were able to show a 50% increase in maximum exercise capacity and a 30% increase in resting cardiac index after venesection from an initial PCV of 0.66 ± 0.01 to 0.58 ± 0.01 $L \cdot L^{-1}$. Heart rate, minute ventilation and arterial

blood gases showed similar responses to exercise before and after venesection.

Table 1.3: Haemodynamic measurements in erythrocytosis

Author	Patients	Number	PCV L/L	PA mmHg	CI L/min/m^2	R_s dynes.s/cm^5	R_p	CI(ex)	PA(ex)	R_s(ex)	R_p(ex)
Weisse et al 1975	Hypoxic lung dis	12	0.62	46	2.8	1739	803				
			0.50	38	2.8	1677	690				
			0.44	38	3.0	1534	684				
Rakita et al 1965	Hypoxic lung dis	15	0.56	32	2.3	1872	730				
			0.54	30	2.3	1850	688				
Segel & Bishop 1966	Hypoxic lung dis	15	0.60	47	3.3	1698	514	4.9	77	1440	636
			0.44	43	3.5	1512	442	5.2	72	1440	529
Harrison et al 1973	Hypoxic lung dis	10	0.63	25				7.22	51.6		
			0.48	23				8.68	41.6		
Wallis et al 1986	Hypoxic lung dis	12	0.61	41	3.1						
			0.50	39	3.4						
Segel & Bishop 1967	P. vera	15	0.63	26	4.2	1504	124	5.9	40	1291	136
			0.47	23	4.1	1464	110	6.7	35	1058	101

PA: mean pulmonary artery pressure; CI: cardiac index; R_s: systemic vascular resistance; R_p: pulmonary vascular resistance; (ex): during exercise

1.3.2 Vascular occlusive episodes

Vascular complications are common and consist of both arterial and venous occlusion. These have been reported by a number of authors[49-54].

Arterial complications were present in 34% of 200 patients presenting to the Hammersmith Hospital with PV[50]. There were 39 cerebrovascular, 10 coronary, and 25 peripheral vascular events in 68 patients. The peripheral vascular events included 15 cases of digital artery involvement with sudden onset of ischaemia and 10 cases of femoral artery occlusion. Values for PCV overall are not given, but the 2 reported cases had haemoglobin concentrations of 16.7 and 19.0 g/dL.

Erythrocytosis is recognised as a risk factor for acute arterial occlusion and steps to reduce PCV in the acute surgical management of these occlusions are recommended[55].

Pearson and Wetherley-Mein[54] described 56 vascular occlusive episodes in 69 patients with PV in a period of 332 patient-years. These were made up of 28 arterial events: 2 mesenteric, 4 coronary, 15 cerebral and 7 lower limb; and 28 venous: 18 deep vein, 9 superficial vein and 1 retinal vein thromboses. The risk of a vascular occlusive event increased with increasing PCV, being 0.2 per 10 years with PCV 0.4 to 0.44, 0.92 with PCV 0.45 to 0.49, 2.29 with PCV 0.50 to 0.55, 3.33 with PCV 0.55 to 0.59 and 7.50 with PCV greater than 0.6 $L \cdot L^{-1}$.

Arterial complications are thought to be due to reduced flow as a consequence of increased whole-blood viscosity[52,53], although PV often has associated thrombocytosis which may exacerbate the occlusive tendencies. Arterial occlusion is described in both PV and secondary erythrocytosis.

Venous thrombosis was reported in 28% of the Hammersmith group[50]. The majority of these were superficial thrombophlebitis (30/66 events) and deep vein thrombosis (25/66 events). Pulmonary embolism, portal vein, and subclavian vein thrombosis were reported in a few instances. Dormandy and Edelman[51] described a relationship between deep vein thrombosis and viscosity. 11/52 patients who developed deep vein thrombosis after surgery had 21% higher whole-blood viscosity than those who did not. Similar pathogenetic mechanisms to those in arterial disease are thought to be responsible.

1.3.3 Cerebrovascular accidents

Epidemiologic and post-mortem studies have shown a significant increase in the incidence of strokes with increase in PCV. Data from the Framingham study[56] show that the relative risk of a cerebral infarction with haemoglobin concentrations greater than 15 g/dL in men and greater than 14 g/dL in women is 1.97 times that in individuals with a lower haemoglobin concentration. The risk of cerebral infarction was also increased with hypertension and smoking.

A post-mortem study from Japan[57] showed that the incidence of cerebral infarction was 6.6% with PCV less than 0.3 $L \cdot L^{-1}$, increasing to 43.6% with PCV between 0.46 and 0.50 $L \cdot L^{-1}$, and 63.6% with PCV greater than 0.51 $L \cdot L^{-1}$. Other risk factors assessed included the severity of atherosclerosis and hypertension. Increasingly severe atherosclerosis was additive to the effects of PCV, but hypertension did not appear to add to the incidence of cerebral infarction. The authors suggested that the optimal PCV was between 0.41 and 0.46 $L \cdot L^{-1}$ in individuals aged under 78 years and between 0.36 and 0.40 $L \cdot L^{-1}$ in older individuals.

The incidence of cerebral infarction in patients with secondary erythrocytosis is unknown, although anecdotal evidence suggests an increased incidence. Rosove et al[34] followed a cohort of 40 adult patients with cyanotic congenital heart disease for a mean of 5.1 years. Their patients had PCV in the range of 0.58 to 0.70 $L \cdot L^{-1}$. Five patients died during follow-up, one of pneumonia and four "suddenly" without a specified cause of death. Only three autopsies were obtained and cerebral micro-infarction was evident in one.

1.3.4 Cerebral blood flow

Other neurological complications are common in erythrocytosis[58]. These include headache (in up to 60% of individuals with erythrocytosis), vertigo (in between 30 and

50%), tinnitus (3 to 10%), visual symptoms (10 to 30%) and paraesthesiae (10 to 50%).

There is convincing evidence that cerebral blood flow is dependent upon the PCV[59-64] and that reduction in PCV improves cerebral blood flow and abolishes the majority of neurological symptoms described in erythrocytosis[59,60,64-66]. Thomas et al[59] have shown that lowering the PCV from a mean of 0.536 $L \cdot L^{-1}$ to 0.455 $L \cdot L^{-1}$ increased the cerebral blood flow by 73%. The initial mean cerebral blood flow was 37.9, compared to a normal value of 69.1 $mL \cdot 100g\ tissue^{-1} \cdot min^{-1}$. Subsequent studies by the same and other authors have shown similar findings[60,64-66].

The level to which the PCV should be reduced was addressed by Thomas et al[59]. They showed that cerebral blood flow was low in 17 of 19 subjects with PCV greater than 0.50, but low in only 2 of 21 subjects with PCV less than 0.46 $L \cdot L^{-1}$. In the range 0.46 to 0.50 $L \cdot L^{-1}$, 14 of 25 had normal and 11 low cerebral blood flow. This suggested that the accepted range of PCV during venesection programmes (0.47 to 0.50 $L \cdot L^{-1}$) may be too high for optimal cerebral blood flow and that aiming at lower levels of PCV during venesection may be beneficial.

A contrary view has been proposed on the grounds that the brain has inherent vascular regulatory mechanisms to ensure adequate oxygen supply[62]. The low cerebral blood flow in erythrocytosis may be due to increased arterial oxygen content and not a consequence of hyperviscosity. Brown and Marshall[64] studied patients with hyperviscosity due to paraproteinaemia and

failed to show a correlation between cerebral blood flow and viscosity. A group of 7 patients with leukaemia, increased blood viscosity and anaemia were shown to have cerebral blood flow appropriate to their level of anaemia. Reduction in viscosity by plasmapheresis showed a similar lack of correlation between viscosity and cerebral blood flow. This was thought to demonstrate that regulatory mechanisms maintain normal cerebral oxygen transport despite increased plasma or whole blood viscosity.

1.3.5 Cerebral function

Measurements of cerebral function in erythrocytosis have been made to quantify the neurological symptoms experienced. Psychometric tests of alertness in 24 patients with PCV greater than 0.46 (mean 0.536) $L \cdot L^{-1}$ demonstrated that a standardised score for alertness was considerably lower than that for matched controls (-3.3 ± 4.2 compared to 0.0 ± 2.9). Sixteen patients underwent venesection to mean PCV 0.479 $L \cdot L^{-1}$ with cerebral blood flow increasing from 44.3 to 56.9 $mL \cdot 100g\ tissue^{-1} \cdot min^{-1}$. The alertness score improved by a mean of 2.82 units with good correlation between the alertness score and cerebral blood flow[61].

1.4 Pathophysiology

The effects of erythrocytosis are predominantly due to increased whole-blood viscosity[52,53,64]. The major determinants of

whole-blood viscosity are plasma viscosity, temperature, PCV and shear-induced deformation of red blood cells[67].

1.4.1 Viscosity

The PCV is the dominant influence on whole-blood viscosity. Begg and Hearns[68] showed that the logarithm of whole-blood viscosity increased linearly with PCV over the range 0.20 to 0.60 $L \cdot L^{-1}$.

This can be represented as:

$$\log(vis) = k + k^1 \times H$$

Where *vis* is the whole-blood viscosity, k a constant close to plasma viscosity in value, k^1 a constant which varies with shear rate and H is PCV [69].

The flow through a tube may be approximated by Poiseuille's Law:

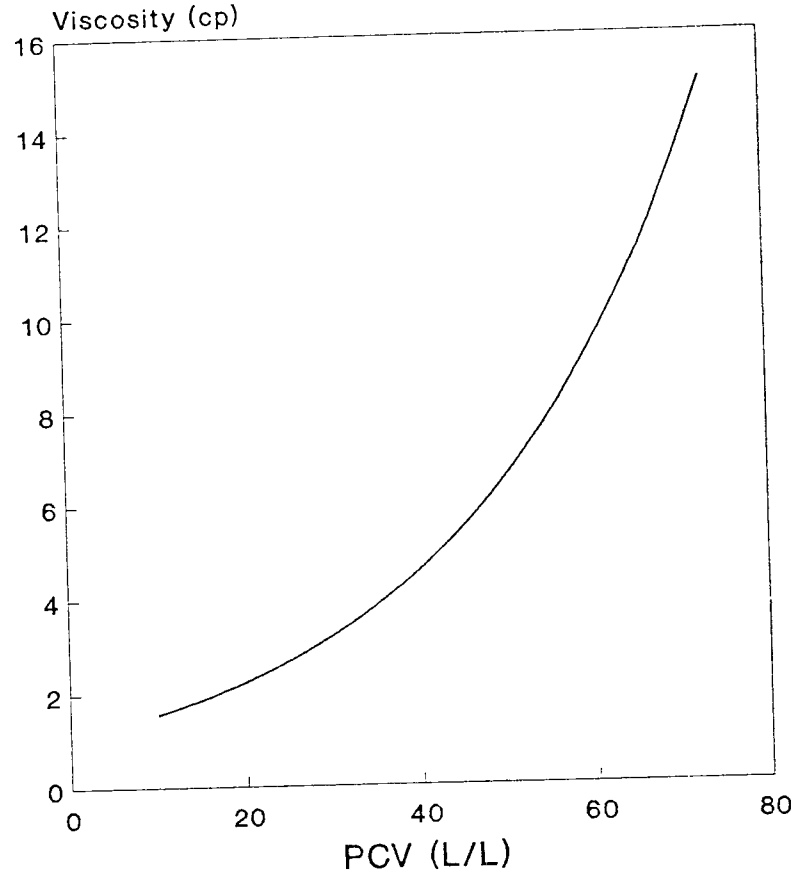
$$\text{Flow} = (P_1 - P_2) \times \pi \times r^4 / (8 \times L \times vis)$$

Where P_1 and P_2 are the arterial and venous pressures, r the radius of the vessel and L the length.

From this it can be seen that organ blood flow is inversely related to viscosity, as well as being dependent on inherent characteristics of the vessels.

The relationship between PCV and whole-blood viscosity is portrayed in **figure 1.3**[70].

Figure 1.3: Plot of whole blood viscosity against increasing PCV



Redrawn from Wells, Merrill; 1962

It can be seen that whole-blood viscosity increases in a near linear fashion to values of PCV about 0.50 $L \cdot L^{-1}$, followed by an exponential rise as the PCV rises higher[12,70].

Organ blood flow should therefore fall inversely with increase in PCV. There is, however, evidence that there are in vivo compensatory mechanisms to overcome the increase in apparent peripheral resistance caused by the increased viscosity. These include increased cardiac output, increased blood volume, vasodilatation and auto-regulation[64,71].

1.4.2 Oxygen transport

Oxygen delivery to tissues is dependent upon cardiac output (tissue blood flow) and oxygen carriage by the blood. The carriage of oxygen in blood depends upon the amount dissolved in plasma (0.0225 mL $O_2 \cdot 100$ mL $blood^{-1} \cdot kPa\ PO_2^{-1}$), which is insignificant at normal barometric pressures and inspired oxygen concentrations, and the amount bound to haemoglobin:

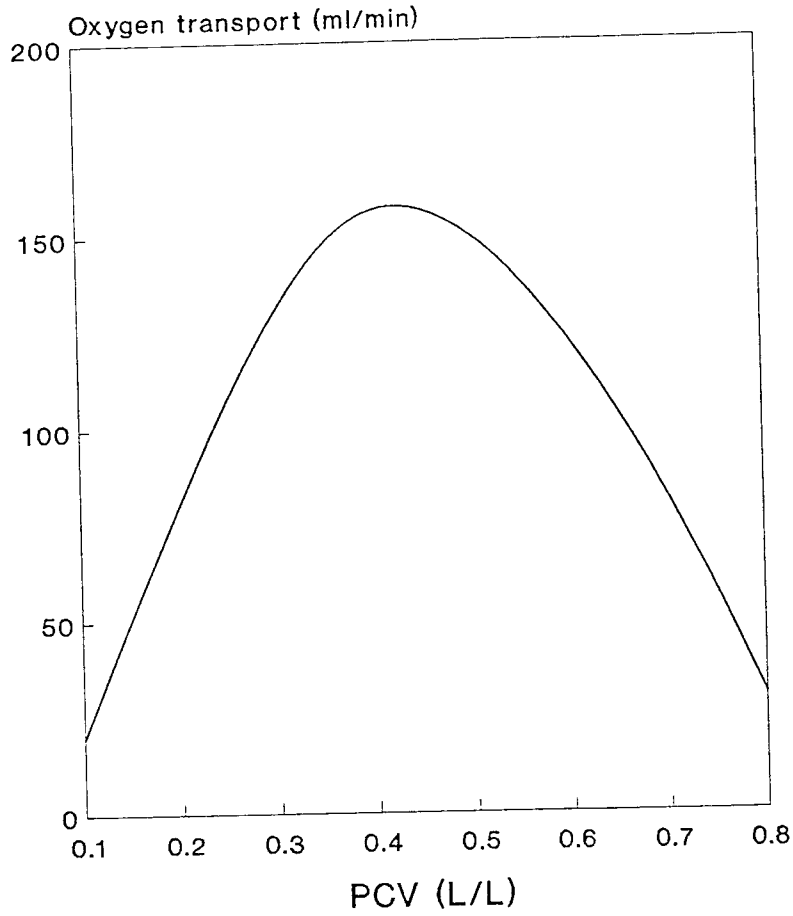
$$1.39 \times [Hb] \times S_aO_2 \text{ mL}/ 100 \text{ mL blood}$$

where [Hb] is the haemoglobin concentration (g/dL), and S_aO_2 the fractional arterial oxygen saturation of haemoglobin[72]. Haemoglobin concentration is thus an important determinant of tissue oxygen delivery[73,74].

Increasing PCV provides opposing forces for oxygen delivery to the tissues. On the one hand, increased PCV increases oxygen carriage by increasing haemoglobin concentration; on the other, increasing PCV reduces the tissue perfusion by increasing viscosity.

This paradox has been addressed by Castle and Jandl[75]. By analysing the effects of increasing PCV on blood flow and oxygen carriage, they were able to construct a figure similar to **figure 1.4.** This shows that oxygen transport is reduced at low PCV (i.e., anaemia) and increases to an apogee with PCV approximately 0.36 to 0.42 $L \cdot L^{-1}$ and thereafter oxygen transport falls progressively as PCV increases.

Figure 1.4: Theoretical analysis of oxygen transport related to PCV



This theoretical approach parallels the in vivo findings of workers with regard to cerebral blood flow[59,60,65] and in dogs.

Richardson and Guyton[76] studied anaesthetised dogs in which the PCV was manipulated and demonstrated an inverse correlation between PCV and cardiac output. Calculation of the number of erythrocytes available for oxygen transport showed a maximum when the PCV was close to 0.40 $L \cdot L^{-1}$. Similar findings were shown by Murray et al[77] who demonstrated that oxygen transport was normal when PCV was in the normal range, but inadequate in anaemia or erythrocytosis.

1.5 Venesection

The aims of management in erythrocytosis, of whatever aetiology, are to control the underlying disease and to reduce the effects of erythrocytosis on organ function. Other therapeutic manoeuvres may be required in PV to control other manifestations of the myeloproliferation. The available therapeutic manoeuvres for control of erythrocytosis include venesection and chemotherapy (in PV)[16,43,44,78].

Venesection is the controlled removal of aliquots of red cells either by physical removal of whole blood, with or without volume replacement, or by apheretic techniques with the removal of red cells while plasma is returned to the patient.

1.5.1 Aims

The aims of venesection are to reduce the PCV and hence the whole-blood viscosity to improve tissue perfusion and hence oxygen delivery. This has been shown to improve cerebral blood flow[59,60,65,66], improve symptoms[61,79,80] and to allow resolution of a number of vascular occlusive episodes[54,55,81]. Other benefits, which are more likely to occur in erythrocytosis secondary to hypoxic lung disease include reductions in pulmonary vascular resistance and pulmonary pressures and possible improvement in exercise capacity[3,33,34,45,79-81].

The extent of venesection needs to balance the improvement in tissue perfusion induced by reduced viscosity against the

reduced oxygen carriage caused by the reduction in haemoglobin concentration. The extent to which the PCV must be lowered has not been clearly established.

1.5.2 Complications

Venesection is not without its hazards. The acute complications described following venesection include acute vascular events due to thrombotic occlusion of vessels, marked drop in circulating blood volume with hypotension and collapse[55,82]. More chronic complications may arise following venesection with the removal of oxygen-carrying capacity and reduced tissue oxygen delivery and ischaemia. Serial venesection results in iron deficiency, which may produce increased viscosity in its own right, or be associated with the development of other symptoms related to the iron deficiency.

1.5.2.1 Vascular events

Rapid removal of blood volume by venesection, without adequate volume replacement, has been documented to cause a significant number of problems[55,82]. These seem to arise particularly in the elderly and in patients with significant cardiovascular disease. Events described include myocardial infarction, collapse, convulsions and acute renal failure. The postulated mechanism for this is the relatively slow replacement of intravascular volume with fall in cardiac output in the face of sustained PCV and viscosity. This may result in stasis or thrombosis. Caution during venesection is necessary, although

the hazards may be reduced by balanced infusion of normal saline or dextran to block the effects of reactive thrombocytosis[55].

1.5.2.2 Oxygen carrying capacity

Reduction in oxygen-carrying capacity is more likely to produce problems in patients with erythrocytosis secondary to hypoxic lung disease or cyanotic congenital heart disease. Oxygen delivery to tissues is composed of oxygen carrying capacity (i.e. oxygen transported bound to haemoglobin) and tissue perfusion. As has been shown previously, venesection and reduction in PCV results in improved tissue perfusion and the benefit of this has to be balanced against the reduced oxygen carriage.

The evidence for improved cerebral blood flow and pulmonary haemodynamics after venesection has been presented. Measurement of regional blood flow in other organs conforms to these findings. Resting calf blood flow was unchanged after venesection PCV 0.61 to 0.51 $L \cdot L^{-1}$, however peak calf blood flow during reactive hyperaemia was increased by 17% at one and 21% at seven days after venesection. Calculated oxygen transport was reduced by 20% at rest, but unchanged during reactive hyperaemia[80]. This confirms that improved regional tissue perfusion compensates for decreased oxygen carrying capacity.

1.5.2.3 Fe deficiency

Iron deficiency is a consequence of repeated venesection and may be a desirable result as this will reduce erythropoiesis and thus increase time between venesections. Whole blood viscosity has been shown to increase as erythrocyte size falls[70]. This may be due to decreased deformability of erythrocytes which is necessary for passage through capillaries. Hutton[83] showed that whole blood viscosity increased in erythrocytotic patients treated by venesection. This has led to the recommendation that iron deficiency be prevented during venesection for erythrocytosis. Subsequent studies[84-86] have shown that whole blood viscosity was unchanged whether iron-deficient or replete at comparable PCV. In patients with erythrocytosis secondary to hypoxia, however, oxygen transport has been shown to be decreased by 11% at a constant PCV of 0.50 $L \cdot L^{-1}$ when mean corpuscular haemoglobin fell from 30 to 20 pg as a consequence of iron deficiency[85].

Iron deficiency is thus desirable in PV, but may be deleterious in secondary erythrocytosis when oxygen transport is paramount.

Patients with erythrocytosis secondary to cyanotic congenital heart disease have been shown to fall into two groups[34,35]. One group maintains a stable elevated PCV with very few symptoms, whereas the other requires frequent venesections to maintain a stable PCV. The latter group frequently develops

symptoms of hyperviscosity, which are associated with iron deficiency, so-called "decompensated erythrocytosis". Correction of the iron-deficient state results in rapid increase in PCV and hyperviscosity[34].

1.6 Optimal level of PCV

A controversy in the management of erythrocytosis by venesection revolves around the level of PCV to which venesection should be conducted. The PCV for optimal function has neither been established in individuals with erythrocytosis secondary to hypoxia, nor in those with erythrocytosis which is primary (PV) or secondary to some other process, but in the presence of normal cardiac and respiratory function.

Common-sense, and accepted practice, suggest that returning the PCV to near the normal range of approximately 0.42 to 0.47 $L \cdot L^{-1}$ is adequate. There is certainly evidence that levels of PCV greater than 0.55 $L \cdot L^{-1}$ are associated with unacceptably high viscosity, markedly reduced cerebral blood flow and a large increase in the incidence of complications due to erythrocytosis. The studies of Weisse et al[4] in patients with hypoxic lung disease suggested that reducing the PCV to approximately 0.50 $L \cdot L^{-1}$ was beneficial in terms of haemodynamic function and that levels lower than this did not produce further haemodynamic improvement.

There is, however, a considerable body of evidence which suggests that the frequently accepted target for venesection of between 0.45 and 0.50 $L \cdot L^{-1}$ is suboptimal. This evidence includes the data cited from the Framingham study[56] and other epidemiogic investigations demonstrating increased vascular, particularly cerebrovascular, morbidity with PCV greater than 0.40 $L \cdot L^{-1}$. Cerebral blood flow studies have shown similar trends with improved cerebral blood flow found when the PCV is between 0.40 and 0.45 $L \cdot L^{-1}$. Theoretical and other experimental analyses have similarly suggested that the optimal combination of haemoglobin and cardiac output in terms of oxygen transport is found when the PCV lies between approximately 0.36 and 0.44 $L \cdot L^{-1}$.

There are no studies which have prospectively examined the functional effects of systematically reducing the PCV from high levels to low normal levels in the region of 0.40 $L \cdot L^{-1}$ in patients in whom effects of cardiac or pulmonary disease can be dissociated from the effects of erythrocytosis.

Chapter 2

Objectives and hypothesis

The aim of the study was to prospectively investigate the effects of a graded venesection programme on individuals with erythrocytosis. This was to attempt to define the optimal PCV that would enable patients to function as normally as possible.

The hypothesis was that graded venesection to PCV levels of 0.50 $L \cdot L^{-1}$, and then 0.40 $L \cdot L^{-1}$ in patients with erythrocytosis, but no significant cardiac or respiratory disease, would result in improved function. This was to be judged on the grounds of clinical, haematological, rheological, pulmonary function, exercise and cerebral blood flow changes.

The discussion in the previous chapter has shown evidence that erythrocytosis is deleterious in terms of organ perfusion and oxygen transport. Procedures to measure these variables include cerebral or calf blood flow and exercise testing. Cerebral, and other organ, blood flow studies measure perfusion, but not necessarily oxygen delivery. The effects of impaired perfusion and oxygen delivery are most likely to be evident when organ function is stressed. Exercise poses an easy stress to

administer, but may be affected by confounding factors such as impaired cardiovascular or respiratory responses.

The management of relative erythrocytosis is completely different to that of absolute erythrocytosis[14]. The study was thus aimed at investigating individuals with absolute erythrocytosis only.

Entry into this study was restricted to individuals with absolute erythrocytosis but normal or near normal cardiac and respiratory function to allow us to use exercise testing as an objective measure of tissue perfusion and oxygen delivery.

Exercise responses in individuals with respiratory or cardiac disease are likely to be affected by the disease process as well as by the erythrocytosis. While these patients pose an important clinical group, we felt that the problems of erythrocytosis in them should be addressed once the hypotheses had been addressed in less compromised individuals. We felt that results from individuals with erythrocytosis, but no other significant disease, could provide pointers for further studies, but that the results from this selected group of patients could not be extrapolated to patients with erythrocytosis as a whole without further evaluation.

Chapter 3

Methods

3.1 Criteria for enrolment

Requirements for inclusion in the study were that the patients should have absolute erythrocytosis with near normal cardio-respiratory function. PCV at presentation had to be greater than 0.55 $L \cdot L^{-1}$ and red cell mass equal to or greater than 38 $mL \cdot kg^{-1}$.

Screening assessment was by history, physical examination, electrocardiograph, chest X-ray, spirometry, full lung volumes, single breath diffusing capacity, full blood count and measurement of red cell mass and plasma volume.

Because exercise was to be a major part of the study, individuals who were unable to perform cycle ergometry for reasons of physical deformity or disabling peripheral vascular disease were not considered for enrolment. For the same reason, patients who did not have normal or near normal lung function and clinically normal cardiovascular systems, apart from controlled hypertension, were not enrolled.

The study was approved by the Ethics and Research Committee of the University of Cape Town and Groote Schuur Hospital. Subjects gave informed consent before participating in the study.

3.2 Procedure

The study was designed so that patients would act as their own controls. Each subject was fully investigated on three occasions. The first set of studies were done at presentation. The studies were repeated after controlled venesection to a target PCV of 0.50 $L \cdot L^{-1}$, and then again when the PCV was 0.4 $L \cdot L^{-1}$.

After the initial studies, patients were seen at weekly intervals in the Haematology Clinic at which time their PCV was reduced by 300-500 mL venesections. They were restudied after the PCV had been stabilised at each of the two target levels for at least one week.

Patients were encouraged to continue normal activities during the study period with no restrictions placed upon diet or exercise, although beginning a formal exercise programme was discouraged.

Once the PCV had been stabilised at the target value, patients underwent the series of investigations. Patients came to the hospital in the morning after an overnight fast, at which time blood for haematological and biochemical analyses were drawn. They then reported to the Respiratory Clinic laboratories

for pulmonary function testing, followed by incremental and steady state exercise testing. Cerebral blood flow studies were usually done on the following morning.

3.3 Clinical evaluation

Prior to each testing session the patients were clinically evaluated by history and physical examination. Particular emphasis was placed on symptoms such as headache, early morning confusion or "thick-headedness", ability to concentrate and vascular complications. Examination was aimed at the cardiovascular and central nervous systems to evaluate the effects of decreasing PCV on perfusion, known vascular complications and haemodynamic function.

3.4 Haematology

Haematological studies included full blood count (Coulter Counter S-Plus, Coulter Electronics, Hialeah, Florida, USA) measuring haemoglobin concentration, red cell indices such as mean corpuscular volume (MCV), and white cell and platelet counts. PCV was measured in duplicate by the capillary technique using a calibrated microcentrifuge and standardised reader (Hawksley, England). Whole blood viscosity was measured using the Brookes-Wellfield cone and plate rheometer (Brookfield Engineering Laboratories, Stroughton, Massachusetts, USA). Red

cell volume was measured using a chromium-labelled red cell technique[15].

3.5 Pulmonary function testing

Lung volumes were determined using a water-sealed spirometer (Expirograph, Godart-Statham, Bilthoven, Holland) with measurement of functional residual capacity by helium dilution. Diffusing capacity for carbon monoxide was estimated by the single breath technique (Transfer Test, PK Morgan, Chatham, Kent, UK). Criteria of the American Thoracic Society[87] for reproducibility of spirometric variables were applied. Reference values for volumes, spirometry and diffusing capacity were those validated for use in our laboratory[88-90].

3.6 Cerebral blood flow

Cerebral blood flow was determined using a ^{133}Xe wash-out technique[91], in which patients rebreathed a gas mixture containing oxygen and ^{133}Xe while maintaining a constant end-tidal carbon dioxide tension. Clearance curves were then obtained over each cerebral hemisphere and values for blood flow in the fast clearing tissue, predominantly grey matter, derived by computer. The mean of left and right hemispheral blood flow (normal range >50 $mL \cdot 100g\ tissue^{-1}$) was taken.

3.7 Exercise testing

3.7.1 Incremental protocol

Incremental exercise testing was carried out by means of the "Stage 1" test described by Jones[92]. This involved cycle ergometry (Monark 668, Vyborg, Sweden) with workload increments of 100 kilopond·metres·minute^{-1} (kp·m·min^{-1}).

The subject came to the exercise laboratory and changed into appropriate clothing, following which electrodes were placed in a modified CM_5 configuration for heart rate monitoring. After an initial period of resting measurement, the subject pedalled the ergometer at a cadence of 50 rpm, in time with a metronome. The workload was increased by 100 kp·m·min^{-1} every minute until the subject could no longer maintain the required cadence.

Measurements made included heart rate, ventilation (dry gas meter; Parkinson-Cowan CD4, Manchester, UK), blood pressure, end-tidal PCO_2 (infra-red CO_2 analyser; Mk 901/2, PK Morgan, Chatham, Kent, UK) and arterial oxygen saturation (HP47201A, Hewlett-Packard, Palo Alto, California, USA).

Outputs from the electrocardiograph, dry gas meter and gas analysers were recorded on a chart recorder (Mingograf 82, Siemens-Elema, Sweden). Results were calculated off-line using standard formulae[92]. The data were entered into a personal computer (Tektronix 4052, Beaverton, Oregon, USA) and plotted (Tektronix 4662) using a custom-written BASIC program.

Maximum workload achieved, heart rate and ventilation were compared to standard predicted values (see **appendix 1** for details). The "ventilatory turnpoint" was determined by inspection of the plot of minute ventilation against workload[93].

3.7.2 Steady state protocol

Steady state measurements (Jones' "Stage 2/3"[92]) were made to accurately calculate gas exchange and cardiac output. Recordings were made at rest and during steady state exercise at a workload of 30% of the maximum workload achieved during the incremental exercise test. Steady state was determined after at least 3 minutes of exercise by the presence of stable mixed expired gas fractions and heart rate fluctuation of less than 5 beats·min^{-1} over a 30 s period.

Mixed expired oxygen (Model S3A oxygen analyser, Applied Electrochemistry, Sunnyvale, California, USA) and carbon dioxide fractions were measured from a 15 L expired gas mixing chamber. Blood gases and pH were measured using arterialised capillary ear-lobe blood sampling (ABL2, Radiometer, Copenhagen, Denmark). Cardiac output was measured by the indirect Fick method using an equilibrium carbon dioxide rebreathing technique[94,95]. Outputs were recorded on the chart recorder as in "Stage 1" testing and results calculated using standard formulae[92], which are outlined in **appendix 2.**

3.8 Statistics

Results obtained from each level of PCV were compared by one-way analysis of variance, using the Scheffe technique to test for significance at the 5% level.

Chapter 4

RESULTS

4.1 Patients

Nine patients with PCV greater than 0.55 $L \cdot L^{-1}$ were enrolled. Four had polycythaemia vera (PV), diagnosed using standard criteria[13] and 5 had erythrocytosis presumed secondary to smoking[38,39], the diagnosis being made on a history of current heavy smoking when other possible causes of erythrocytosis had been excluded[21]. Basic demographic data at presentation are shown in **table 4.1.**

The patients presented to the Department of Haematology or Respiratory Clinic in a variety of ways (**table 4.1**). Four were found to have erythrocytosis on routine testing following presentation with unrelated complaints. The remaining 5 were diagnosed as having erythrocytosis after presenting with symptoms or signs related to erythrocytosis.

Those with occlusive vascular disease had their presenting problem controlled by the referring surgeons or physicians, but did not receive any specific therapy for the erythrocytosis prior to enrolment in the study. The patients with PV did not receive

therapy other than phlebotomy during the study period. Patients with erythrocytosis secondary to smoking ceased to smoke during the study. No patient was receiving a drug which could influence exercise performance.

Table 4.1: Patient data at presentation

Patient	Sex	Age yr	Ht cm	Wt kg	Diag	Smoke pk·yr	Reason for presentation
1	F	60	162	55	PV	0	Ischaemic toes
2	M	43	172	88	PV	0	Vertigo, pruritus
3	M	51	180	77	PV	0	Diabetes, routine FBC
4	M	57	173	59	PV	10	Routine examination
5	M	40	158	48	Sm	10	Acute arterial occlusion
6	M	32	192	83	Sm	30	Deep venous thrombosis
7	M	34	166	46	Sm	25	Hypertension, routine FBC
8	M	39	169	60	Sm	20	Back pain, routine exam
9	M	39	180	74	Sm	20	Investigated for narcolepsy

Sm: Erythrocytosis secondary to smoking; pk·yr: pack·years

Two subjects were studied at presentation and after venesection to PCV of 0.5 $L \cdot L^{-1}$ only. Patient 8 withdrew because of problems related to the time needed off work to attend for the regular venesection sessions. Patient 9 was withdrawn when the diagnosis of narcolepsy was made and he was started on methylphenidate as it was thought that this may influence the

outcome of exercise testing. Neither patient had suffered any adverse effects during the period of venesection.

4.2 Clinical evaluation

All subjects had near normal clinical examinations at presentation, with abnormal features being those directly attributable to erythrocytosis. All had symptoms suggestive of expanded red cell mass including lethargy, early morning headache and mental clouding. Physical signs included plethora, peripheral cyanosis, and impaired capillary filling in most, and evidence of mild peripheral vascular disease in 2 patients. There were no signs of cardiac decompensation or disabling vascular disease.

Chest radiographs were essentially normal, apart from rather plethoric lung fields and mild hyperinflation in some cases. Electrocardiographs were similarly within normal limits, apart from left ventricular hypertrophy in a patient with controlled systemic hypertension.

Repeat clinical evaluation at a PCV of 0.5 $L \cdot L^{-1}$ and subsequently at 0.4 $L \cdot L^{-1}$ demonstrated an improvement in well-being and activity levels and a marked diminution of symptoms in all subjects. Peripheral circulatory problems were uniformly resolved. These clinical features had begun to improve by the time PCV reached 0.5 $L \cdot L^{-1}$ and had improved further when the PCV was 0.4 $L \cdot L^{-1}$. Four subjects were reassessed one month after

completion of the study, during which time they had been maintained at a PCV of 0.4 $L \cdot L^{-1}$ and each demonstrated further improvement in subjective well-being.

No adverse effects of venesection were apparent and there were no acute vascular occlusive events or episodes of hypotension during the venesection programme.

4.3 Haematologic studies

At presentation, all subjects had elevated PCV in the range 0.56 to 0.70 $L \cdot L^{-1}$ (**table 4.2**). The haemoglobin concentrations were elevated in the range 182 to 234 $g \cdot L^{-1}$. White cell counts were normal in the 5 subjects with erythrocytosis secondary to smoking and were mildly elevated (19.0 to 25.9 x $10^9 \cdot L^{-1}$) in 3 of those with PV. Platelet counts were similarly normal in smokers and elevated (524 to 1093 X $10^9 \cdot L^{-1}$) in 3 of the patients with PV.

Mean corpuscular volumes at presentation were in the range 78 to 102 (92.7 ± 13.3; mean ± sd) fL. Serum vitamin B_{12} and serum and red cell folate levels were normal. Iron stores as reflected by serum iron, total iron binding capacity, percentage saturation of transferrin and ferritin levels were normal.

Red cell mass and plasma volume estimations confirmed the presence of absolute erythrocytosis, with red cell mass at presentation in the range 38 to 67 $mL \cdot kg^{-1}$ (**table 4.2**). In 2 cases measurement of red cell mass could not be performed because of the need to intervene with urgent treatment of the

erythrocytosis. Both of these patients had PV and thus unequivocal absolute erythrocytosis.

Table 4.2: Haematologic data at presentation

Patient	Hb $g \cdot L^{-1}$	PCV $L \cdot L^{-1}$	WCC $x10^9 \cdot L^{-1}$	Pl $x10^9 \cdot L^{-1}$	MCV fL	RCM $mL \cdot kg^{-1}$	PlV $mL \cdot kg^{-1}$
1	207	0.67	19.3	552	78.5		
2	184	0.58	16.6	797	88.1	38	36
3	234	0.70	10.3	352	80.7	67	26
4	210	0.66	19.1	901	72.1		
5	182	0.56	6.8	115	102.0	38	39
6	211	0.60	6.2	286	111.0	44	36
7	194	0.59	9.1	231	102.0	52	39
8	190	0.56	7.1	202	101.0	38	37
9	189	0.58	7.1	199	99.0	38	36
Mean	200	0.61	11.3	404	92.7		
sd	17	0.05	5.5	282	13.3		

WCC: White cell count; Pl: Platelet count; RCM; red cell mass; PlV: plasma volume

The venesection programme resulted in achievement of the target PCV for each subsequent period of testing. This fall in PCV was associated with an appropriate fall in haemoglobin. Haemoglobin concentration was 200 ± 17 $g \cdot L^{-1}$ at presentation, 162 ± 6 $g \cdot L^{-1}$ at PCV of 0.5 $L \cdot L^{-1}$ ($p<0.001$ compared to presentation, **table 4.3**), and fell to 129 ± 8 $g \cdot L^{-1}$ at a PCV of 0.4 $L \cdot L^{-1}$ ($p<0.0001$ compared to presentation, **table 4.4**).

The mean WCC remained unchanged throughout the study period. The platelet count increased following venesection in 3 of the 4 patients with PV. This increase was particularly marked at the PCV level of 0.4 $L \cdot L^{-1}$. The platelet count in subjects 2 and 4 increased markedly with presentation counts of 797 and 901 $x10^9 \cdot L^{-1}$ increasing to 1760 and 1960 $x10^9 \cdot L^{-1}$ respectively by the third study day. No untoward sequelae of these thrombocytoses occurred. Platelet counts in patients with smoking-induced erythrocytosis remained in the normal range.

Mean corpuscular volume tended to fall during the venesection programme from 92.7 ± 13.3 at presentation to 84.2 ± 16.6 fL when the PCV was 0.4 $L \cdot L^{-1}$. In three patients (2, 3, and 4) the MCV fell markedly to between 65.2 and 72.1 fL. Iron studies were initially normal in all cases and repeat studies showed the development of marked iron deficiency in these patients. Ferritin values fell to between 10 and 15 $ng \cdot mL^{-1}$. Iron studies were unfortunately not performed on all patients during the follow-up studies.

Table 4.3: Haematologic data on second study day

Patient	Hb $g \cdot L^{-1}$	PCV $L \cdot L^{-1}$	WCC $x10^9 \cdot L^{-1}$	Pl $x10^9 \cdot L^{-1}$	MCV fL
1	160	0.51	6.0	522	81.0
2	158	0.48	25.3	754	76.1
3	157	0.50	12.6	513	72.0
4	157	0.50	21.3	1090	71.5
5	164	0.50	6.5	150	97.0
6	166	0.52	4.7	163	107.0
7	158	0.48	5.5	360	101.0
8	171	0.50	5.4	248	101.0
9	170	0.50	10.7	218	98.7
Mean	162	0.50	10.9	446	89.5
sd	6	0.01	7.6	313	14.1

Table 4.4: Haematologic data on third study day

Patient	Hb	PCV	WCC	Pl	MCV
	$g \cdot L^{-1}$	$L \cdot L^{-1}$	$x10^9 \cdot L^{-1}$	$x10^9 \cdot L^{-1}$	fL
1	117	0.36	4.1	309	82.2
2	128	0.40	25.0	1760	65.2
3	122	0.38	14.3	705	68.2
4	131	0.42	9.9	1960	72.1
5	137	0.40	6.3	293	96.6
6	140	0.42	5.0	395	107.0
7	126	0.39	6.5	271	98.4
Mean	129	0.40	10.2	813	84.2
sd	8	0.02	7.4	732	16.6

Whole blood viscosity was markedly elevated at 10.7 ± 3.3 cP at presentation (normal range 4.9 to 6.9 cP, measured at a shear stress of 100 s^{-1}). Following venesection, whole blood viscosity fell to 8.0 ± 1.1 when measured at a PCV of 0.5 $L \cdot L^{-1}$ ($p<0.05$ compared to presentation) with a further fall at PCV of 0.4 $L \cdot L^{-1}$ to 6.2 ± 0.8 ($p<0.005$ compared to presentation, and $p<0.05$ compared to PCV 0.5). This is seen in **table 4.5** and **figure 4.1**

Table 4.5: Whole blood viscosity

Patient	Initial cP	PCV=0.5 cP	PCV=0.4 cP
1	13.8	6.1	6.1
2	8.5	8.4	7.1
3	17.2	9.4	5.5
4	8.9	9.7	6.8
5	8.1	7.5	4.9
6	8.5	7.6	6.0
7	7.4	7.4	6.9
8	12.9	8.2	
9	10.8	7.3	
Mean	10.7	8.0	6.2
sd	3.3	1.1	0.8
p (Init vs 0.5)	<0.05		
(0.5 vs 0.4)		<0.05	
(Init vs 0.4)	<0.005		

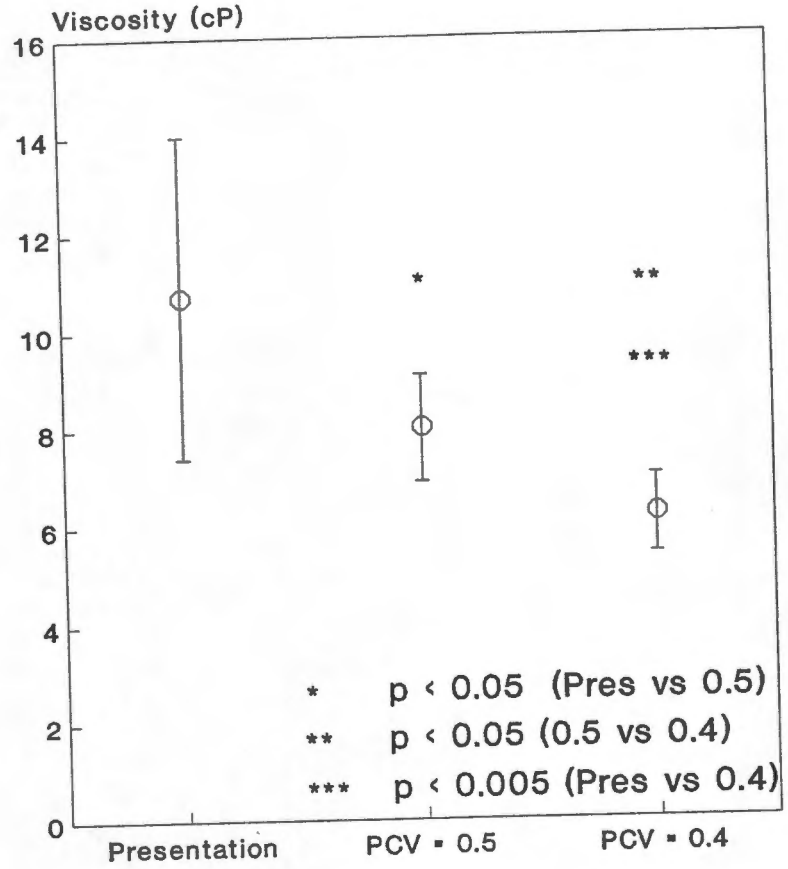


Figure 4.1: Plot of whole blood viscosity against PCV

4.4 Pulmonary function testing

All subjects had measurement of lung volumes and mechanics. These were compared to reference values currently used in the pulmonary function laboratory[88,89]. The data obtained at presentation are shown in **table 4.6.** Patient 5 had moderate airflow obstruction, but this was thought to be insufficient to account for his erythrocytosis and was unlikely to significantly

affect his exercise capacity. Repeat volumes and mechanics on each study day showed no significant change as a consequence of venesection.

Table 4.6: Pulmonary function at presentation

Patient	1		2		3		4		5		6		7		8		9	
	mL	%	mL	%	mL	%	mL	%	mL	%	mL	%	mL	%	mL	%	mL	%
IC	1990		2680		2970		2160		1620		3840		1780		2170		3924	
ERV	940		1040		920		2050		1620		2170		2180		2660		1340	
VC	2930	105	3720	82	3890	85	4210	101	3240	84	6010	104	3960	99	4830	102	5264	106
FRC	2370		2400		2700		4180		3520		3880		3390		4600		2970	
RV	1430		1360		1780		2130		1900		1710		1210		1940		1630	
TLC	4360	105	5080	83	5670	87	6340	100	5140	94	7720	103	5170	93	6770	112	6894	103
RV/TLC (%)	32.8	102	26.8	107	31.4	108	33.6	99	37.0	127	22.2	101	23.4	84	28.7	102	23.6	91
FEV1	2160	99	3100	90	3420	97	3060	94	1620	52	4430	96	3260	98	3200	93	3850	99
FVC	2920	107	3840	85	4050	88	4210	101	3250	84	6100	105	3990	100	4580	105	4995	101
FEV1/FVC (%)	74.0	92	80.7	105	84.4	111	72.7	97	49.8	64	72.6	92	81.7	101	69.9	90	77.1	99

Data expressed as actual measured values and percentage of predicted, using standard formulae.

Arterial blood gases were in the normal range at presentation, and whenever measured during the study period. Arterial oxygen saturations were above 92% in all cases (table 4.7).

Table 4.7: Arterial P_aO_2 and S_aO_2 on study days

	Presentation		PCV = 0.5		PCV = 0.4	
Patient	P_aO_2 kPa	S_aO_2 %	P_aO_2 kPa	S_aO_2 %	P_aO_2 kPa	S_aO_2 %
1	12.8	98	13.9	98	12.3	97
2	10.9	97	11.7	97	9.5	92
3	12.0	96	12.5	97	12.3	96
4	12.4	96	10.8	95	10.9	96
5	12.4	96	10.3	96	15.5	98
6	14.8	98	13.7	98	12.4	97
7	12.2	95	12.8	98	13.9	98
8	11.8	97	12.1	97		
9	11.9	97	13.6	98		
Mean	12.4	96	12.2	97	12.4	96
sd	1.1	2	1.3	1	1.9	2

4.4.1 Diffusing capacity

Diffusing capacity for carbon monoxide (T_lCO_{sb}) was markedly increased at presentation in all but one patient. T_lCO_{sb} was 123.4 ± 21.2% and transfer coefficient (KCO) similarly increased at 128.0 ± 27.4% of the predicted value[90] (**table 4.8**). At PCV 0.5 $L \cdot L^{-1}$ both had fallen, to 97.8 ± 8.2% and 101.6 ± 16.6%

respectively (**table 4.9**). There was a further but smaller fall when the PCV was reduced to 0.4 $L \cdot L^{-1}$ (**table 4.10**).

Table 4.8: Diffusing capacity at presentation

Patient	T_lCO_{sb} $ml \cdot mmHg^{-1} \cdot min^{-1}$	% pred	KCO $ml \cdot mmHg^{-1} \cdot min^{-1} \cdot L^{-1}$	% pred
1	31.4	142.1	7.7	156.2
2	33.5	112.4	6.0	122.4
3	42.2	137.0	7.6	165.2
4	40.1	147.4	7.0	159.1
5	22.3	86.1	4.9	98.0
6	51.1	132.4	6.1	113.5
7	39.0	139.8	7.3	137.7
8	33.2	112.2	5.2	103.6
9	33.5	101.5	4.9	96.2
Mean	36.3	123.4	6.3	128.0
SD	8.1	21.2	1.1	27.4

Table 4.9: Diffusing capacity with PCV 0.5

Patient	T_lCO_{sb}	% pred	KCO	% pred
	$ml \cdot mmHg^{-1} \cdot min^{-1}$		$ml \cdot mmHg^{-1} \cdot min^{-1} \cdot L^{-1}$	
1	23.5	106.3	5.5	110.5
2	30.6	102.7	6.1	124.2
3	32.4	105.2	5.6	122.2
4	24.9	91.5	4.8	109.1
5	21.9	84.6	4.7	94.0
6	38.2	99.1	5.0	93.8
7	29.7	106.5	5.4	101.9
8	28.4	95.9	4.2	83.1
9	29.2	88.5	3.8	75.9
Mean	28.8	97.8	5.0	101.6
SD	5.0	8.2	0.7	16.6

Table 4.10: Diffusing capacity at PCV 0.4

Patient	T_lCO_{sb}	% pred	KCO	% pred
	$ml \cdot mmHg^{-1} \cdot min^{-1}$		$ml \cdot mmHg^{-1} \cdot min^{-1} \cdot L^{-1}$	
1	19.4	87.8	4.7	95.3
2	27.8	93.3	5.4	110.0
3	30.6	99.4	5.4	117.2
4	20.5	75.4	3.4	76.8
5	18.4	71.0	4.2	83.2
6	35.0	90.8	4.6	86.3
7	26.2	93.9	5.1	96.2
Mean	25.4	87.4	4.7	95.0
SD	6.3	10.4	0.7	14.5

Diffusing capacity fell more markedly relative to the change in haemoglobin concentration when venesection reduced PCV from presenting values to 0.5 $L \cdot L^{-1}$ than when PCV was reduced from 0.5 to 0.4 $L \cdot L^{-1}$. This is shown in **figure 4.2.** There was a significant correlation between change in T_lCO_{sb} and change in haemoglobin concentration when PCV was decreased from presenting values to 0.5 $L \cdot L^{-1}$ (**figure 4.3,** $r = 0.72$, $p = 0.03$), but no correlation between changes in T_lCO_{sb} and haemoglobin when PCV was reduced from 0.5 to 0.4 $L \cdot L^{-1}$ (**figure 4.4,** $r = -0.05$, $p = 0.92$).

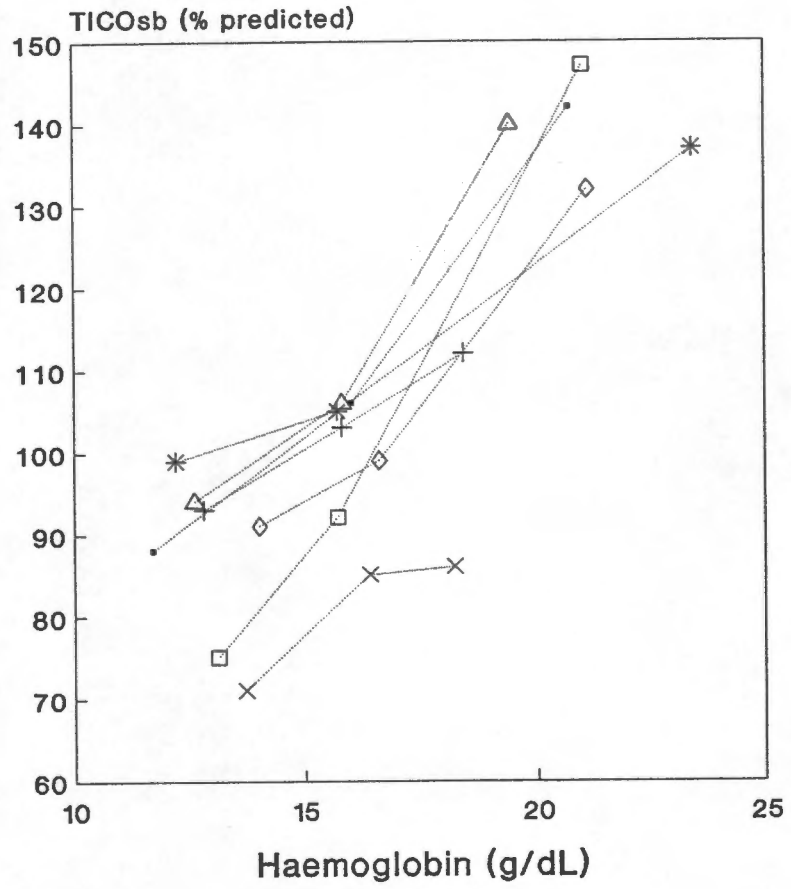


Figure 4.2: Diffusing capacity as percentage predicted, compared to haemoglobin at presentation and following venesection

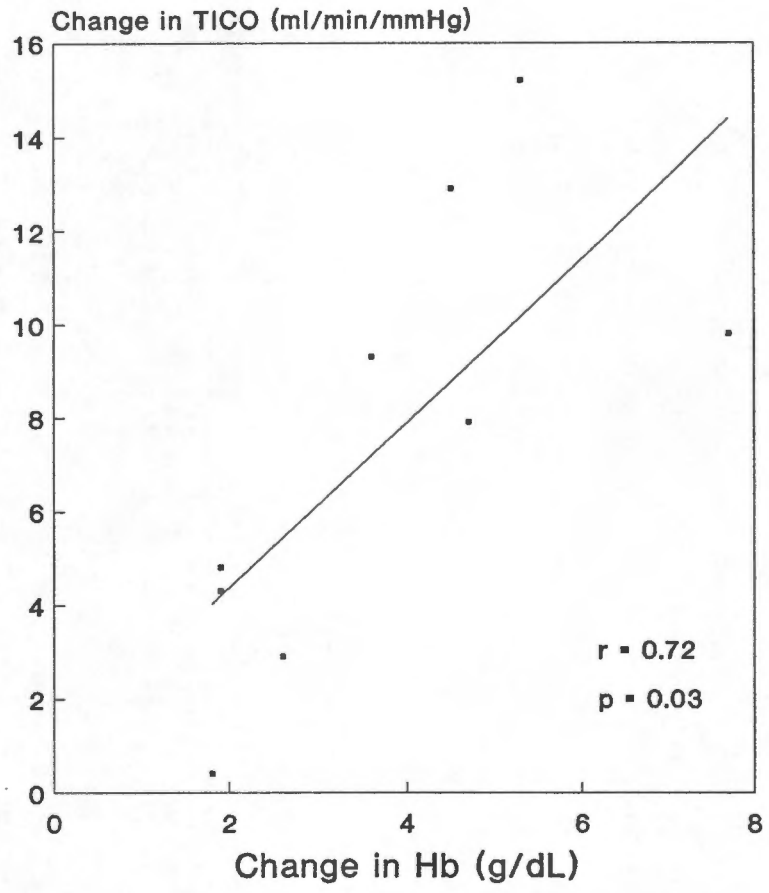


Figure 4.3: Diffusing capacity change between presentation and PCV 0.5

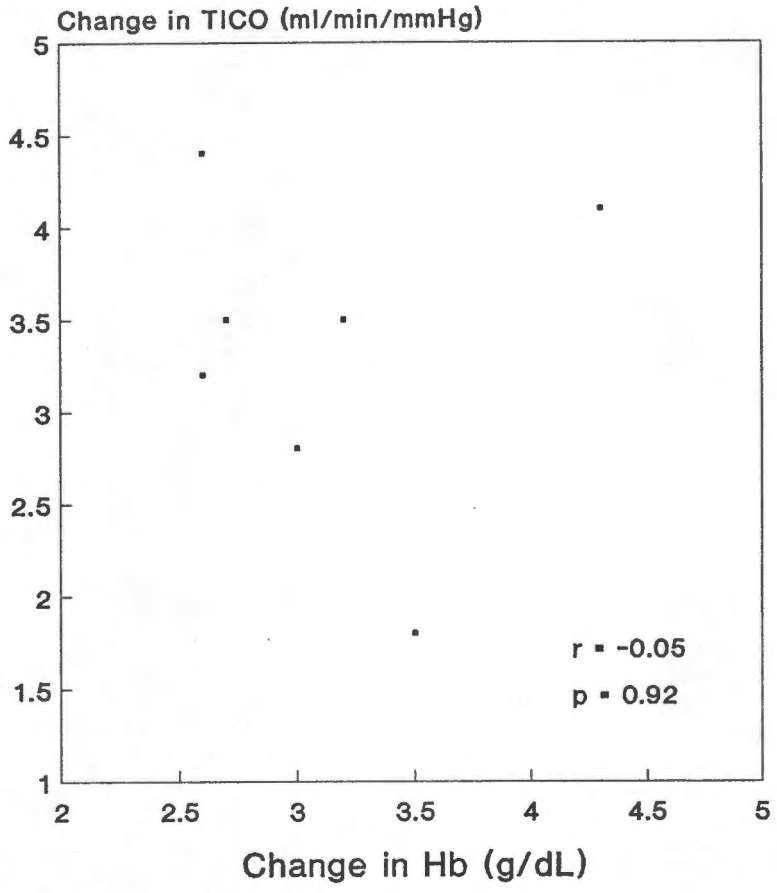


Figure 4.4: Diffusing capacity change between PCV 0.5 and 0.4

4.5 Cerebral blood flow

Cerebral blood flow could not be measured in one patient because of technical difficulties, but was measured on the day following exercise and pulmonary function testing in all other patients. CBF was below the normal value of 50 $mL \cdot min^{-1} \cdot (100g\ tissue)^{-1}$ in 7 of the 8 patients at presentation with mean CBF

being 39.8 ± 5.3 (**table 4.11**). There was a moderate increase in CBF to 47.9 ± 9.5 following venesection to a PCV of 0.5 $L \cdot L^{-1}$. At PCV 0.4 $L \cdot L^{-1}$ CBF was within the normal range in 7 of 8 patients with mean CBF 58.2 ± 14.2 $mL \cdot min^{-1} \cdot (100g\ tissue)^{-1}$ ($p < 0.001$ compared to presenting values). The differences in CBF between presentation and PCV 0.5 $L \cdot L^{-1}$ and PCV 0.5 and 0.4 $L \cdot L^{-1}$ were not significant however.

Table 4.11: Cerebral blood flow

Patient	Initial	PCV=0.5	PCV=0.4
	$mL \cdot min^{-1} \cdot (100g\ tissue)^{-1}$		
1	35.5	52.5	57.0
2	46.7	49.0	89.1
3	36.0	57.9	56.4
4	33.3	33.3	49.2
5	42.5	50.6	57.5
6	35.6	37.4	48.0
7	42.2	41.9	50.0
9	46.4	59.7	
Mean	39.8	47.9	58.2
sd	5.3	9.5	14.2
p (Init vs 0.5)		NS	
(0.5 vs 0.4)			NS
(Init vs 0.4)		<0.001	

Cerebral blood flow correlated inversely with whole blood viscosity (**figure 4.5**, $r = -0.45$, $p = 0.03$). There was a similar significant inverse relationship between cerebral blood flow and arterial oxygen content, see **figure 4.6** ($r = -0.66$, $p = 0.0006$).

Figure 4.7 shows that there was no correlation between whole blood viscosity and cerebral oxygen transport, calculated as the product of cerebral blood flow and arterial oxygen content.

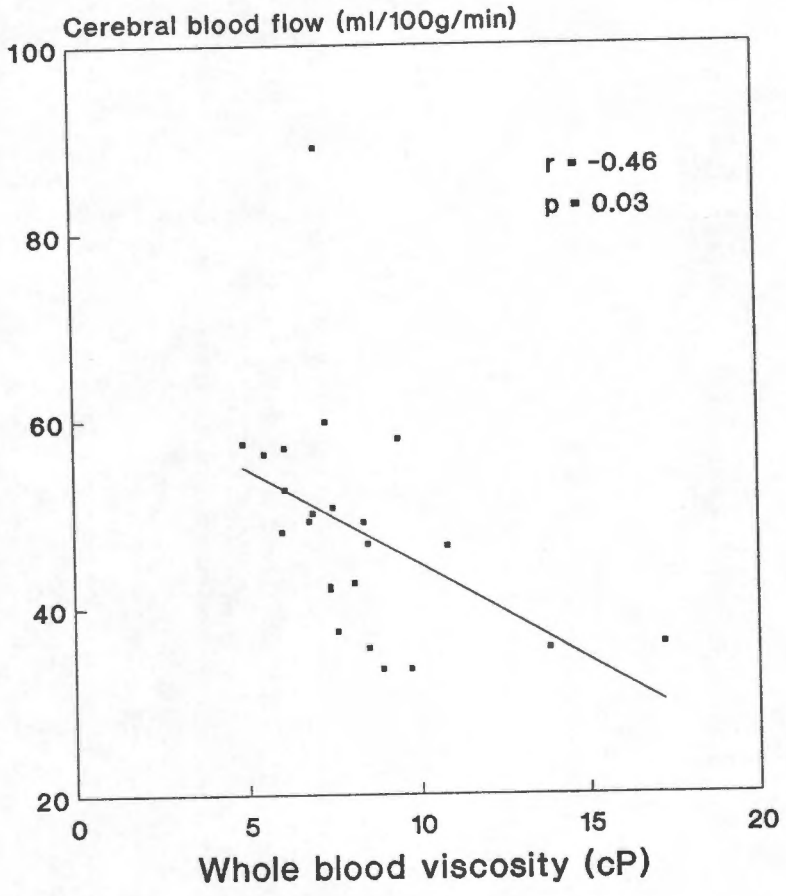


Figure 4.5: Relationship between whole blood viscosity and cerebral blood flow

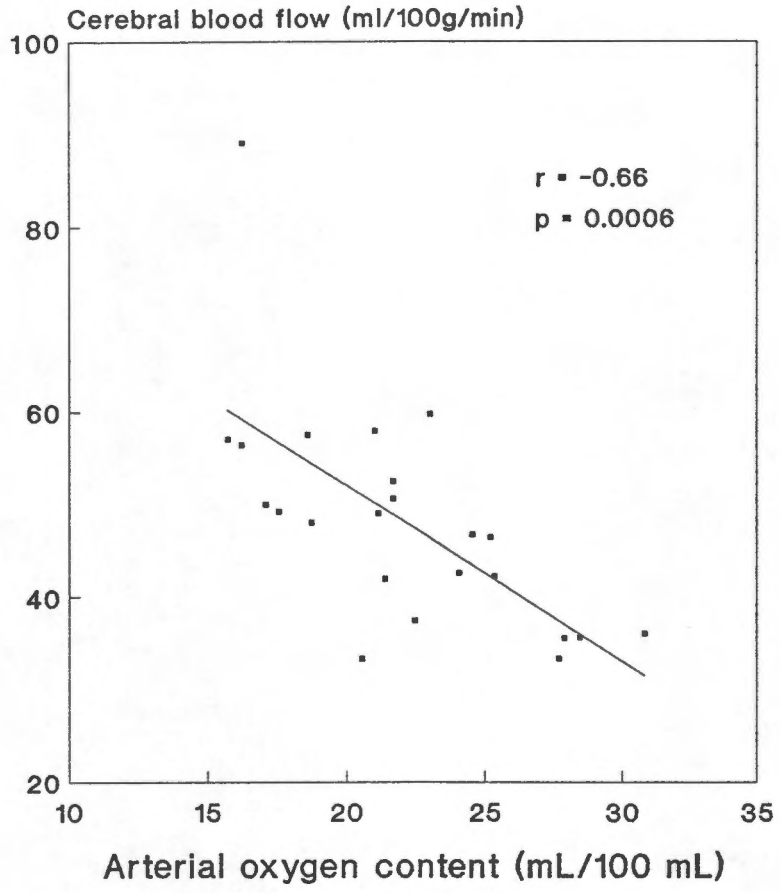


Figure 4.6: Arterial oxygen content and cerebral blood flow

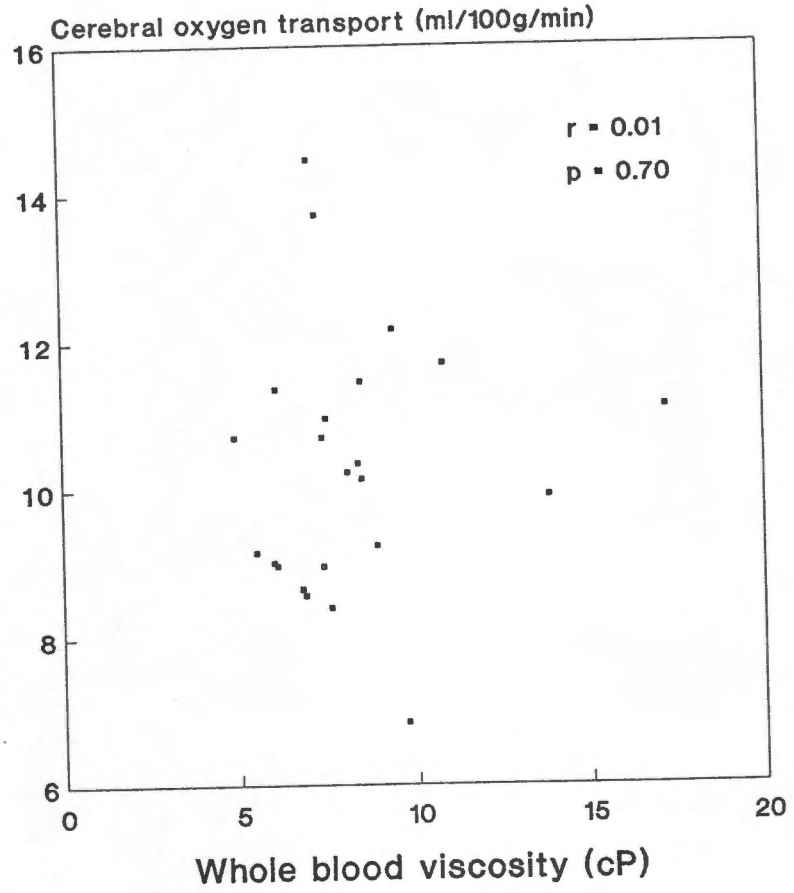


Figure 4.7: Calculated cerebral oxygen transport and whole blood viscosity

4.6 Exercise testing

4.6.1 Incremental exercise

All subjects were able to exercise on the study day. During incremental exercise all subjects were limited by leg fatigue and not dyspnoea or other symptoms. Maximum exercise capacity at presentation was 79.7 ± 22.3% of predicted[92], which was mildly

reduced (**table 4.12**). Heart rate at maximum exercise was close to age-predicted maximum[96] in all except patient 3. Only two patients reached their ventilatory limit, but neither complained of dyspnoea terminating exercise. Heart rate and blood pressure responses to exercise were normal. Overall, the ventilatory turnpoint was lower than the expected values (60 to 75% of maximum exercise).

Table 4.12: Incremental exercise at presentation

Patient	Workload (% pred)	Heart rate (% pred)	Ventilation (% pred)	Vent TP (% max ex)
1	117	91	73	55
2	100	102	129	40
3	64	68	54	60
4	92	90	45	50
5	94	96	97	62
6	50	84	40	62
7	67	88	60	50
8	57	97	78	65
9	77	86	51	65
mean	79.7	89.0	69.7	56.6
sd	22.3	9.7	28.6	8.5

Vent TP: Ventilatory turnpoint; % pred: % predicted maximum; % max ex: % maximum exercise

There was no significant change in maximum exercise capacity following venesection (**figure 4.8a**), although there was some individual variability. Overall maximum exercise capacity was 78.3 ± 14.3% of predicted at PCV 0.5 $L \cdot L^{-1}$ (**table 4.13**) and

76.4 ± 23.9% at PCV 0.4 $L \cdot L^{-1}$ (**table 4.14**). All patients reported that exercise felt easier, although no formal evaluation of perceived exertion was done. Similarly, there was no significant difference between heart rate at maximum exercise or maximum ventilation between presentation and PCV of 0.5 and 0.4 $L \cdot L^{-1}$ (**Figure 4.8b and 4.8c**).

The ventilatory turnpoint increased from 56.6 ± 8.5% of maximum exercise at presentation to 68.8 ± 10.8 at PCV 0.5 $L \cdot L^{-1}$ ($p<0.05$ compared to presentation) and 72.6 ± 11.5% at PCV 0.4 $L \cdot L^{-1}$ ($p<0.01$ compared to presentation) (**Figure 4.8d**).

Table 4.13: Incremental exercise, PCV = 0.5 $L \cdot L^{-1}$

Patient	Workload (% pred)	Heart rate (% pred)	Ventilation (% pred)	Vent TP (% max ex)
1	83	88	78	60
2	92	104	129	65
3	64	63	56	70
4	92	80	45	66
5	71	101	90	50
6	56	79	43	78
7	67	90	57	65
8	95	103	70	85
9	85	96	51	80
mean	78.3	89.4	68.7	68.8
sd	14.3	13.5	27.4	10.8

Table 4.14: Incremental exercise, PCV 0.4 $L \cdot L^{-1}$

Patient	Workload (% pred)	Heart rate (% pred)	Ventilation (% pred)	Vent TP (% max ex)
1	100	94	80	70
2	92	102	131	50
3	64	65	59	70
4	108	91	66	75
5	71	91	89	83
6	56	84	43	85
7	44	88	40	75
mean	76.4	87.6	72.6	72.6
sd	23.9	11.5	31.2	11.5

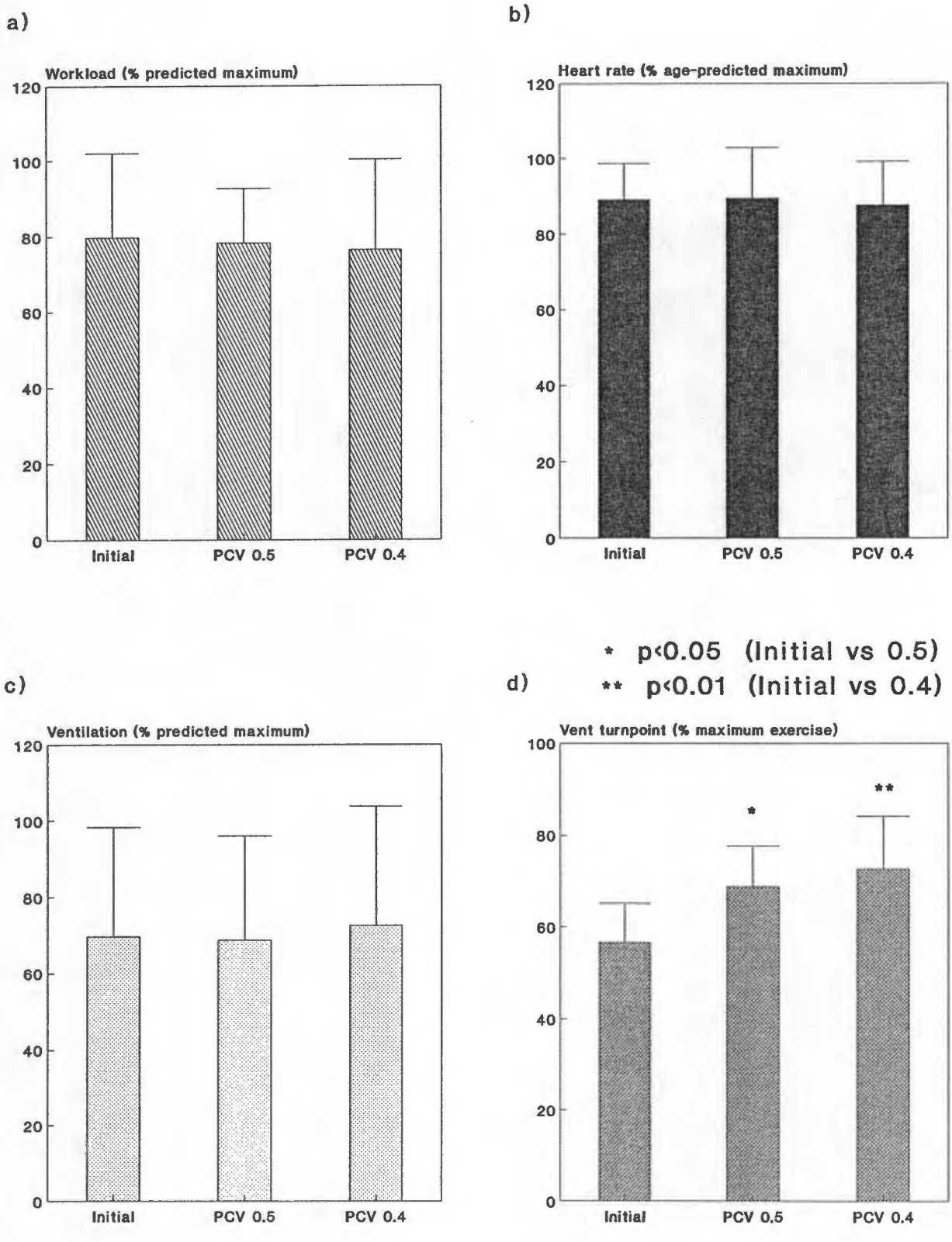


Figure 4.8: Incremental exercise testing data

4.6.2 Steady state exercise

Measurements were made during steady state at rest and while exercising at approximately 30% of the maximum workload achieved on the preceding incremental test. The workloads during exercise ranged from 100 to 400 $kp \cdot m \cdot min^{-1}$, and most subjects exercised at the same workload on each occasion. The workload during exercise when PCV was 0.4 $L \cdot L^{-1}$ was slightly, but not significantly, reduced compared to initial exercise. Resting and exercise oxygen consumption were not different as the PCV fell (**table 4.15**). Heart rate during exercise was slightly lower when PCV was 0.4 $L \cdot L^{-1}$ than at presentation or when PCV was 0.5 $L \cdot L^{-1}$. This difference was not significant. There was a similar small fall in cardiac output during exercise and a small increase in arterial-mixed venous oxygen content difference (**table 4.15**).

Blood gas and pH measurements showed a trend for less fall in pH and bicarbonate during exercise after venesection. These differences were small, however.

There were no changes in other measures of gas exchange such as dead space-tidal volume ratio or shunt fraction at rest or during exercise.

Table 4.15: Steady state exercise data

Patient	Initial				PCV = 0.5					PCV = 0.4				
	Rest		Exercise		Rest		Exercise			Rest		Exercise		
	mean	sd	mean	sd	mean	sd	mean	sd	p	mean	sd	mean	sd	p
Workload (kpm/min)	0		356	90	0		300	122	NS	0		271	125	NS
VO2 (mL/min)	303	64	1170	421	293	59	1099	314	NS	253	57	1071	361	NS
Heart rate (b/min)	88	14	134	17	90	21	129	21	NS	78	16	118	14	NS
Cardiac output (L/min)	5.5	1.8	10.8	2.7	7.0	2.4	11.1	3.3	NS	5.8	2.6	9.3	2.4	NS
C(a-v)O2 (mL/100 mL)	5.8	1.3	10.8	2.3	4.6	1.6	10.3	2.6	NS	4.9	1.7	11.8	2.0	NS
pH	7.40	0.04	7.35	0.03	7.39	0.04	7.38	0.06	NS	7.41	0.02	7.37	0.04	NS
PO2 (kPa)	12.7	1.3	13.9	1.7	12.4	1.3	12.6	1.9	NS	12.7	1.8	13.2	1.7	NS
PCO2 (kPa)	4.9	0.6	4.3	1.0	4.9	0.5	4.5	0.9	NS	5.0	0.3	4.5	0.5	NS
[HCO3-] (mmol/L)	21.6	2.3	17.1	4.3	21.7	2.4	19.2	2.7	NS	22.8	1.4	18.9	1.5	NS

sd: standard deviation; p: p compared to presentation
C(a-v)O2: arterial-mixed venous oxygen content difference
[HCO3-]: plasma bicarbonate concentration

Chapter 5

DISCUSSION

In response to venesection, all the subjects in this study experienced a striking subjective improvement in that they were better able to perform day-to-day tasks, had an increase in exercise tolerance and mental alertness, diminution in lethargy and abolition of headache. This improvement in symptoms was marked by the time their PCV reached 0.5 $L \cdot L^{-1}$ and further improvement was evident once stabilisation had occurred at 0.4 $L \cdot L^{-1}$. These observations were supported by clinical objective evidence of better tissue perfusion, with marked improvement in pre-existing signs of peripheral vascular insufficiency. Changes in cerebral blood flow mirrored these findings.

Concurrently, all laboratory measurements were markedly improved. The fall in whole blood viscosity was most rapid in the period between presentation and when the PCV reached 0.5 $L \cdot L^{-1}$, being almost in the normal range, and the further small decrement to achieve normality occurred with the PCV stabilised at 0.4 $L \cdot L^{-1}$. These changes are due to the reduction in red cell mass as other factors known to effect rheology were within the normal range at the start of the study.

Similarly, the results of the exercise tests show that reduction in the PCV, and hence oxygen carrying capacity per unit volume, was not associated with any deterioration in exercise tolerance nor demonstrable change in cardiac output during steady state exercise. This observation suggests that tissue oxygen delivery was improved, despite the reduced oxygen carrying capacity, and implies more effective microvascular perfusion resulting from the reduced viscosity. Further evidence supporting improved tissue perfusion is the progressive increase in the ventilatory threshold on incremental exercise[97,98]. This fact is also consistent with enhanced oxygen delivery to metabolising tissue, with reduction in glycolysis-induced hydrogen ion production and more effective removal of metabolic breakdown products as a consequence of improved rheology: this benefit was clearly evident at 0.5 $L \cdot L^{-1}$ and was more marked at 0.4 $L \cdot L^{-1}$. An alternative explanation for this phenomenon could be improved physical fitness as a result of training. Such a postulate can be discounted as the subjects were essentially sedentary and maintained similar degrees of activity throughout the study. Moreover, maximum exercise capacity was unchanged in the group as a whole. There was some individual variability in maximum exercise capacity which amounted to approximately one workload on the protocol used. This is almost certainly due to the 'stepped' increment in workload of 100 $kp \cdot m \cdot min^{-1}$. A 'ramp' protocol or smaller 'step' in workload would have allowed for greater precision in measurement.

Cardiac output and arterial-mixed venous oxygen content difference during steady state exercise did not change while oxygen consumption was similar at each level of PCV. This implies that increased oxygen carriage to the tissues in erythrocytosis did not result in appropriate tissue oxygen uptake, supplying further evidence that high PCV results in impaired tissue perfusion.

Cerebral blood flow was shown to increase as PCV and whole blood viscosity fell. There was a strong relationship between arterial oxygen content and cerebral blood flow and there was no correlation between cerebral oxygen transport and viscosity. This suggests that oxygen delivery to the brain is maintained as a result of autoregulation, in keeping with the findings of Friedland[62] and Marshall[64]. Impaired oxygen transport to the brain cannot thus be blamed for the marked neuropsychiatric symptoms that are frequently found in erythrocytosis[58,61]. Impaired microcirculation, regional ischaemia, accumulation of metabolites and sludging due to increased viscosity and reduced flow are likely to be responsible for these symptoms. The continued improvement in well-being as PCV falls below 0.50 $L \cdot L^{-1}$ with increasing cerebral blood flow but no increase in oxygen delivery reinforces these postulated mechanisms.

All the data, whether it be clinical, haematological, rheological, or physiological, shows that reduction in PCV below the initial presenting value is beneficial. The results at PCV 0.5 $L \cdot L^{-1}$ are in keeping with a number of previous studies

involving venesection in erythrocytosis due to various causes. Of greater significance is the continued improvement when the PCV is reduced further into the low normal range. In this group of patients with no significant cardiac or respiratory disease there is evidence that cerebral blood flow and tissue perfusion are better at PCV 0.4 $L \cdot L^{-1}$. The results of the exercise tests show that the potential disadvantage of decreased oxygen carriage is offset by better tissue perfusion. Coupled with the theoretical[75] and epidemiological[56,57] data cited previously it appears that the optimal PCV in patients without cardiac or respiratory disease lies close to 0.4 $L \cdot L^{-1}$ and that this should be the target if venesection is undertaken. Iron deficiency may result in symptoms or impaired exercise performance following venesection, although the data is inconsistent[34,35,83-86].

The problem of erythrocytosis secondary to severe pulmonary disease or cyanotic congenital heart disease, although a separate issue, is a cause for considerable clinical concern given the extensive evidence for the marked hyperviscosity that occurs when the PCV exceeds 0.51 to 0.55 $L \cdot L^{-1}$[33,52,56,75,99]. A marked increase in peripheral vascular, coronary and cerebrovascular morbidity prevails under these circumstances.

The recommendations of Perloff et al[35] based on their experience with patients with cyanotic congenital heart disease were that venesection was indicated only when patients had symptomatic hyperviscosity with PCV greater than 0.65 $L \cdot L^{-1}$. Their aim of venesection was to withdraw the minimum blood volume

required to produce symptomatic relief. They also felt that iron deficiency may play an important role in hyperviscosity and suggested that hyperviscosity symptoms with PCV less than 0.65 $L \cdot L^{-1}$ was due to iron deficiency. They described very few vascular or thrombotic complications in their patients.

These recommendations conflict with the findings in the current study in which considerable symptomatic and physiological derangements were present with PCV very much lower than the level of 0.65 $L \cdot L^{-1}$ regarded as the threshold for venesection by Perloff. There is considerable evidence that these recommendations are not appropriate for patients with hypoxic lung disease or polycythaemia vera in which considerable benefit has been found following venesection from levels 0.60 $L \cdot L^{-1}$ and lower[2,45,46,48,79,100].

Pulmonary function tests have been evaluated previously during serial venesection in erythrocytosis, and as shown in this study lung volumes and mechanics remain unchanged after venesection, even when erythrocytosis is secondary to hypoxic lung disease[2,4,45,48,79,100]. Diffusing capacity for carbon monoxide has also been studied[101-105]. In this study, diffusing capacity was shown to be markedly raised compared to the predicted values at the high PCV of presentation, with subsequent fall to close to predicted values following venesection(**figure 4.2**). There is not, however, a linear relationship between change in PCV or haemoglobin and fall in diffusing capacity. The fall seemed particularly marked when PCV fell from presentation to

0.50 $L \cdot L^{-1}$, with a much smaller fall when PCV was further reduced to 0.40 $L \cdot L^{-1}$ (**figures 4.3** and **4.4**).

Diffusing capacity measures the transfer of carbon monoxide across the alveolar-capillary membrane and subsequent uptake by red cells in the pulmonary capillaries[106]. This can be represented as the sum of resistances:

$$1/T_lCO = 1/D_m + 1/\Theta \cdot V_c$$

where D_m represents a membrane component, Θ the reaction rate of CO with haemoglobin and V_c the effects of haemoglobin concentration and pulmonary capillary blood volume. D_m and Θ are unchanged and as haemoglobin concentration does not correlate with changes in diffusing capacity the presumption is that the pulmonary capillary volume is increased in erythrocytosis and falls as PCV returns to within the normal range. This is supported by the data of several workers[104,107]. In patients with PV, Burgess[103] showed that V_c was reduced and postulated that this was due to in situ thromboses in the pulmonary microcirculation. The initial observations of Burgess[103] and Herbert[102] that diffusing capacity correlated well with haemoglobin concentration appear wrong in the light of more recent work, including this study.

Diffusing capacity is frequently used in the assessment of severity of lung disease and is overestimated in erythrocytosis. An equation to correct diffusing capacity in anaemia has been widely used[108]. This equation corrects the diffusing capacity to that which should prevail if haemoglobin concentration were

146 $g \cdot L^{-1}$. In erythrocytosis, however, use of this equation results in a falsely high diffusing capacity[104] and care needs to be exercised when interpreting diffusing capacity values in erythrocytotic patients.

A further separate issue concerns the optimal PCV for athletic performance, since there exists among athletes a belief that there is an advantage to be gained by increasing haematocrit above normal, a practice known as "blood-doping"[109]. Spriet et al[110] demonstrated an increase in maximal oxygen uptake of almost 7% when PCV was boosted from 0.46 $L \cdot L^{-1}$ to 0.51 $L \cdot L^{-1}$ by the re-infusion of three units of freeze-stored blood. This finding supports previous studies[111,112], although conflicting results have been reported[113,114]. The latter authors have been criticised on methodological grounds[109], and there is now consensus that increasing the PCV above normal confers benefit in terms of performance of endurance exercise. We do not consider these findings in athletes to be in conflict with the present study undertaken on patients who were sedentary, middle-aged and suffering from pathological erythrocytosis. Firstly, athletes have an increased capillary bed in the working muscles as a component of physical fitness[115] and secondly, the effects of re-infusion on cerebral blood flow and on longer-term morbidity have not been studied. The criteria by which PCV is judged to be optimum may be different in athletes[116].

Chapter 6

Summary and conclusions

Nine previously untreated patients with erythrocytosis with packed cell volume (PCV) of greater than 0.55 $L \cdot L^{-1}$ were studied at presentation, a second time when the PCV was stabilised at 0.5 $L \cdot L^{-1}$, and again when this value was 0.4 $L \cdot L^{-1}$. Studies included clinical assessment and the measurement of whole blood viscosity, pulmonary function, incremental and steady state exercise testing and cerebral blood flow. Reduction in red cell mass by controlled venesection was associated with symptomatic improvement in all patients. Reduction in PCV from the presenting level of 0.61 ± 0.05 $L \cdot L^{-1}$ to 0.40 ± 0.02 $L \cdot L^{-1}$ resulted in a decrease in whole blood viscosity from 10.7 $\pm$ 3.3 to 6.2 $\pm$ 0.8 cP, increased cerebral blood flow from 39.8 $\pm$ 5.3 to 52.8 $\pm$ 8.3 $mL \cdot 100g\ tissue^{-1}$, and increased ventilatory turnpoint from 56.6 $\pm$ 8.5 % of maximum achieved workload to 72.6 $\pm$ 11.5 %, with no fall in exercise capacity. These changes, which were significant at PCV 0.5 $L \cdot L^{-1}$, were more marked at PCV 0.4 $L \cdot L^{-1}$.

These findings support the hypothesis that in patients with erythrocytosis the increased oxygen carrying capacity consequent upon an expanded red cell mass is without benefit to the patient. On the contrary, it would appear that the dominant influence of

this phenomenon on symptoms and exercise capacity is an adverse one related to impaired tissue perfusion, almost certainly due to hyperviscosity. Thus, in individuals with normal or near normal cardiovascular and respiratory function, marked benefit to metabolising tissues will result from reduction in viscosity consequent upon venesection. Oxygen delivery is thus likely to be improved, notwithstanding the lower oxygen-carrying capacity of blood following venesection. It is notable that reduction in the PCV well below the upper normal limit of 0.47 $L \cdot L^{-1}$ results in further clinical and laboratory improvement and the present study would support 0.4 $L \cdot L^{-1}$ rather than 0.5 $L \cdot L^{-1}$ as a reasonable target in any program of venesection for individuals who are without cardiovascular or respiratory impairment. Iron deficiency may supervene and cause symptoms in its own right. This eventuality requires independent evaluation.

It follows that a reasonable approach in patients with arterial hypoxaemia would be the use of a judicious venesection program, with careful clinical and physiological, including exercise, monitoring to reduce PCV to a level resulting in improved cerebral function but without loss of exercise capacity.

On the basis of this prospective study in which each individual acted as his or her own control, it is possible to conclude that in absolute erythrocytosis reduction in the red cell mass by graded venesection to a packed cell volume of approximately 0.4 $L \cdot L^{-1}$ will result in marked symptomatic

improvement and this is accompanied by achievement of optimal cerebral blood flow and muscle perfusion.

References

1. Wade JPH, Pearson TC, Ross Russell RW, Wetherley-Mein G. Cerebral blood flow and blood viscosity in patients with polycythaemia secondary to hypoxic lung disease. Lancet 1981; 283:689-692.

2. Rakita L, Gillespie DG, Sancetta SM. The acute and chronic effects of phlebotomy on general haemodynamics and pulmonary functions of patients with secondary polycythaemia associated with pulmonary emphysema. Am Heart J 1965; 70:466-475.

3. Segel N, Bishop JM. The circulation in patients with chronic bronchitis and emphysema at rest and during exercise, with special reference to the influence of changes in blood viscosity and blood volume on the pulmonary circulation. J Clin Invest 1966; 45:1555-1568.

4. Weisse AB, Moschos CB, Frank MJ, Levinson GE, Cannilla JE, Regan TJ. Hemodynamic effects of staged hematocrit reduction in patients with stable cor pulmonale and severely elevated hematocrit levels. Am J Med 1975; 58:92-98.

5. Perutz MF. Hemoglobin structure and respiratory transport. Sci Am 1978; 239:68-87.

6. Finch CA, Lenfant C. Oxygen transport in man. N Eng J Med 1972; 286:407-415.

7. Benesch R, Benesch RE. The effect of organic phosphates from the human erythrocyte on the allosteric properties of hemoglobin. Biochem Biophys Res Commun 1967; 26:162.

8. Bunn HF, Jandl JH. Control of haemoglobin function within the red cell. N Eng J Med 1970; 282:1414-1420.

9. Koury ST, Bondurant MC, Koury MJ. Localisation of erythropoietin synthesising cells in murine kidneys by in situ hybridisation. Blood 1988; 71:524-527.

10. Goldberg MA, Dunning SP, Bunn HF. Regulation of the erythropoietin gene: evidence that the oxygen sensor is a heme protein. Science 1988; 242:1412-1415.

11. Ogawa M, Porter PN, Nakahata T. Renewal and commitment to differentiation of hemopoietic stem cells (an interpretative review). Blood 1983; 61:823-829.

12. Erslev AJ, Gabuzda TG. Pathophysiology of blood. 3rd ed. Philadelphia: W.B. Saunders, 1985:

13. Berlin NI. Diagnosis and classification of the polycythaemias. Sem Hematology 1975; 12:339-351.

14. Weinreb NJ, Shih C-F. Spurious polycythemia. Semin Hematol 1975; 12:397-407.

15. International Committee for Standardisation in Haematology . Standard techniques for the measurement of red cell and plasma volume. Br J Haematol 1973; 25:801-814.

16. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic recommendations in polycythemia vera based on polycythemia vera study group protocols. Sem Hematology 1986; 23:132-143.

17. Shamdas GJ, Spier CM, List AF. Myelodysplastic transformation of polycythemia vera: Case report and review of the literature. Am J Hematol 1991; 37:45-48.

18. Najean Y, Deschamps A, Dresch C, Daniel MT, Rain JD, Arrago JP. Acute leukemia and myelodysplasia in polycythemia vera. A clinical study with long term follow-up. Cancer 1988; 61:89-95.

19. Swolin B, Weinfeld A, Westin J. A prospective long-term cytogenetic study in polycythemia vera in relation to treatment and clinical course. Blood 1988; 72:386-395.

20. Silverstein MN. The evolution into and the treatment of late stage polycythemia vera. Semin Hematol 1976; 13:79-84.

21. Balcerzak SP, Bromberg PA. Secondary polycythaemia. Sem Hematology 1975; 12:353-382.

22. Kennedy CA, Griffith HS, Mathisen GE. Erythrocytosis after zidovudine for AIDS. Ann Intern Med 1991; 114:250-251.

23. Karlish AJ, Marshall R, Reid L, Sherlock S. Cyanosis in hepatic cirrhosis. Thorax 1967; 22:555-561.

24. Stanley NN, Woodgate DJ. The circulation, the lung, and finger clubbing in hepatic cirrhosis. Br Heart J 1971; 33:469-472.

25. Dreicer R, Donovan J, Benda JA, Lund J, Degowin RL. Paraneoplastic erythrocytosis in a young adult with an erythropoietin-producing Wilms' tumor. Am J Med 1992; 93:229-230.

26. Trimble M, Caro J, Talalla A, Brain M. Secondary erythrocytosis due to a cerebellar hemangioblastoma: Demonstration of erythropoietin mRNA in the tumor. Blood 1991; 78:599-601.

27. Navarro J, Aguilera A, Liaño F, Pascual J, Ortuño J. Phlebotomy for polycythemia associated with acquired cystic renal disease in a patient on hemodialysis. Nephron 1992; 62:110-111.

28. Sahoo RN, Das BK, Mohapatra MK, Das GC. Polycythemia in renal transplant recipients. Transplant Proc 1992; 24:1772.

29. Horstman D, Weiskopf R, Jackson RE. Work capacity during a 3-wk sojourn at 4,300 m: effects of relative polycythemia. J Appl Physiol 1980; 49:311-318.

30. Robertson RJ, Gilcher R, Metz KF, et al. Effect of simulated altitude erythrocythemia in women on hemoglobin flow rate during exercise. J Appl Physiol 1988; 64:1644-1649.

31. West JB. Respiratory Physiology: the essentials. Baltimore: Williams and Wilkins, 1974:

32. Wagner PD, Rodriguez-Roisin R. Clinical advances in pulmonary gas exchange. Am Rev Respir Dis 1991; 143:883-888.

33. Oldershaw PJ, Sutton MGStJ. Haemodynamic effects of haematocrit reduction in patients with polycythaemia secondary to cyanotic congenital heart disease. Br Heart J 1980; 44:584-588.

34. Rosove MH, Hocking WG, Canobbio MM, Perloff JK, Child JS, Skorton DJ. Chronic hypoxaemia and decompensated erythrocytosis in cyanotic congenital heart disease. Lancet 1986; 2:313-315.

35. Perloff JK, Rosove MH, Child JS, Wright GB. Adults with cyanotic congenital heart disease: hematologic management. Ann Int Med 1988; 109:406-413.

36. Block AJ, Boysen PG, Wynne JW, Hunt LA. Sleep apnea, hypopnea and oxygen desaturation in normal subjects. N Eng J Med 1979; 300:513-517.

37. Zwillich CW, Sutton FD, Pierson DJ, Weil JV. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. Am J Med 1975; 59:343-348.

38. Sagone AL, Balcerzak SP. Smoking as a cause of erythrocytosis. Ann Int Med 1975; 82:512-515.

39. Smith JR, Landaw SA. Smoker's Polycythemia. N Eng J Med 1978; 298:6-10.

40. Jandl JH. Blood. Textbook of Hematology. Boston: Little,Brown and Company, 1987:392-394.

41. Berman W, Wood SC, Yabek SM, Dillon T, Fripp RR, Burstein R. Systemic oxygen transport in patients with congenital heart disease. Circulation 1987; 75:360-368.

42. Brown CD, Kieran M, Thomas LL, Zhao Z-H, Larsen R, Friedman EA. Treatment of azotemic, nonoliguric, anemic patients with human recombinant erythropoietin raises whole-blood viscosity proportional to hematocrit. Nephron 1991; 59:394-398.

43. Golde DW, Hocking WG, Koeffler HP, Adamson JW. Polycythemia: Mechanisms and management. Ann Int Med 1981; 95:71-87.

44. Harrison BDW, Stokes TC. Secondary polycythaemia: its causes, effects and treatment. Br J Dis Chest 1982; 76:313-340.

45. Harrison BDW, Davis J, Madgwick RG, Evans M. The effects of therapeutic decrease in packed cell volume on the responses to exercise of patients with polycythaemia secondary to lung disease. Clin Sci Mol Med 1973; 45:833-847.

46. Wallis PJW, Skehan JD, Newland AC, Wedzicha JA, Mills PG, Empey DW. Effects of erythrapheresis on pulmonary haemodynamics and oxygen transport in patients with

secondary polycythaemia and cor pulmonale. Clin Sci 1986; 70:91-98.

47. Segel N, Bishop JM. Circulatory studies in polycythaemia vera at rest and during exercise. Clin Sci 1967; 32:527-549.

48. Chetty KG, Brown SE, Light RW. Improved exercise tolerance of the polycythemic lung patient following phlebotomy. Am J Med 1983; 74:415-420.

49. Chievitz E, Thiede T. Complications and cause of death in polycythaemia vera. Acta Med Scand 1962; 172:513-523.

50. Barabas AP, Offen DN, Meinhard EA. The arterial complications of polycythaemia vera. Brit J Surg 1973; 60:183-187.

51. Dormandy JA, Edelman JB. High blood viscosity: an aetiological factor in venous thrombosis. Brit J Surg 1973; 60:187-190.

52. Lowe GDO. Blood viscosity, heart attack and stroke. The Croom lecture. Proc Edinburgh Coll Physicians 1985; 3:

53. Lowe GDO. Blood rheology in arterial disease. Clin Sci 1986; 71:137-146.

54. Pearson TC, Wetherley-Mein G. Vascular occlusive episodes and venous haematocrit in primary proliferative polycythaemia. Lancet 1978; ii:1219-1222.

55. Shah DM, Buchbinder D, Balko A, Karmody AM, Leather RP. Use of isovolemic hemodilution in the management of arterial ischaemia in patients with polycythemia. Am J Surg 1981; 142:233-235.

56. Kannel WB, Gordon T, Wolf PA, McNamara P. Hemoglobin and the risk of cerebral infarction: The Framingham study. Stroke 1972; 3:409-420.

57. Tohgi H, Yamanouchi H, Murakami M, Kameyama M. Importance of the haematocrit as a risk factor in cerebral infarction. Stroke 1978; 9:369-374.

58. Silverstein A, Gilbert H, Wasserman LR. Neurologic complications of polycythemia. Ann Int Med 1962; 57:909-916.

59. Thomas DJ, Marshall J, Ross Russell RW, et al. Effect of haematocrit on cerebral blood flow in man. Lancet 1977; 8045:941-943.

60. Thomas DJ, Marshall J, Ross Russell RW, et al. Cerebral blood flow in polycythaemia. Lancet 1977; ii:161-163.

61. Willison JR, du Boulay GH, Paul EA, et al. Effect of high haematocrit on alertness. Lancet 1980; i:846-848.

62. Friedland RP, Grant S. Hematocrit, viscosity and cerebral blood flow. Am Heart J 1979; 97:404-405.

63. Grotta J, Ackerman R, Correia J, Fallick G, Chang J. Whole blood viscosity parameters and cerebral blood flow. Stroke 1982; 13:296-301.

64. Brown MM, Marshall J. Regulation of cerebral blood flow in response to changes in blood viscosity. Lancet 1985; i:604-609.

65. Humphrey PRD, Marshall J, Ross Russell RW, et al. Cerebral blood flow and viscosity in relative polycythaemia. Lancet 1977; ii:873-877.

66. Humphrey PRD, Michael J, Pearson TC. Management of relative polycythaemia: studies of cerebral blood flow and viscosity. Br J Haematol 1980; 46:427-433.

67. Lowe GDO. Blood rheology. Clin Haematol 1987; 1:597-636.

68. Begg TB, Hearns JB. Components in blood viscosity. Clin Sci 1966; 31:87-93.

69. Whittington RB, Harkness J. Whole-blood viscosity as determined by plasma viscosity, hematocrit, and shear. Biorheology 1982; 19:175-184.

70. Stone HO, Thompson HK, Schmidt-Nielsen K. Influence of erythrocytes on blood viscosity. Am J Physiol 1968; 214:913-918.

71. Anon . Polycythaemia due to hypoxaemia: advantage or disadvantage? Lancet 1989; 2:20-22.

72. Gregory IC. The oxygen and carbon monoxide capacities of foetal and adult blood. J Physiol 1974; 236:625.

73. Stainsby WN, Snyder B, Welch HG. A pictographic essay on blood and tissue oxygen transport. Med Sci Sports Exerc 1988; 20:213-221.

74. Warren GL, Cureton KJ. Modeling the effect of alterations in hemoglobin concentration on VO_2max. Med Sci Sports Exerc 1989; 21:526-531.

75. Castle WB, Jandl JH. Blood viscosity and blood volume: opposing influences upon oxygen transport in polycythemia. Sem Hematology 1966; 3:193-198.

76. Richardson TQ, Guyton AC. Effects of polycythemia and anemia on cardiac output and other circulatory factors. Am J Physiol 1959; 197:1167-1170.

77. Murray JF, Gold P, Johnson BL. Systemic oxygen transport in induced normovolaemic anemia and polycythemia. Am J Physiol 1962; 203:720-724.

78. Wasserman LR. The treatment of polycythaemia vera. Sem Hematology 1976; 13:57-78.

79. Dayton LM, McCullough RE, Scheinhorn DJ, Weil JV. Symptomatic and pulmonary response to acute phlebotomy in secondary polycythemia. Chest 1975; 68:785-790.

80. Wallis PJW, Apps MCP, Newland AC, Empey DW. Calf blood flow and oxygen carriage after reversal of polycythaemia secondary to hypoxic lung disease. Thorax 1986; 41:306-310.

81. Shah DM, Powers SR, Bernard HR, Scovill WA, Newell JC, Stratton HH. Increased oxygen uptake following phlebotomy and simultaneous fluid replacement in polycythemic patients. Surgery 1980; 88:868-692.

82. Kiraly JF,III, Feldman JE, Wheby MS. Hazards of phlebotomy in polycythemic patients with cardiovascular disease. JAMA 1976; 236:2080-2081.

83. Hutton RD. The effect of iron deficiency on whole blood viscosity in polycythaemic patients. Br J Haematol 1979; 43:191-199.

84. Pearson TC, Grimes AJ, Slater NGP, Wetherley-Mein G. Viscosity and iron-deficiency in treated polycythaemia. Br J Haematol 1981; 49:123-127.

85. Van de Pette JEW, Guthrie DL, Pearson TC. Whole blood viscosity in polycythaemia: the effect of iron deficiency at a range of haemoglobin and packed cell volumes. Br J Haematol 1986; 63:369-375.

86. Birgegård G, Carlsson M, Sandhagen B, Mannting F. Does iron deficiency in treated polycythemia vera affect whole blood viscosity? Acta Med Scand 1984; 216:165-169.

87. American Thoracic Society . Snowbird workshop on standardisation of spirometry. Am Rev Respir Dis 1979; 119:831-838.

88. Grimby G, Söderholm B. Spirometric studies in normal subjects. III: Static lung volumes and maximum voluntary ventilation in adults with a note on physical fitness. Acta Med Scand 1963; 173:199-206.

89. Schoenberg JB, Beck GJ, Bouhuys A. Growth and decay of pulmonary function in healthy blacks and whites. Resp Physiol 1978; 33:367-393.

90. Cotes JE. Lung Function. Assessment and application in medicine. 4th ed. Oxford: Blackwell Scientific, 1979:

91. Obrist WD, Thompson HK,Jr, King HC. Determination of RCBF by inhalation of ^{133}Xenon. Circ Res 1967; 20:124-135.

92. Jones NL, Campbell EJM. Clinical Exercise Testing. 2nd ed. Philadelphia: Saunders, 1982:

93. Wasserman K, Whipp BJ, Koyal SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol 1973; 35:236-243.

94. Collier CR. Determination of mixed venous CO_2 tensions by rebreathing. J Appl Physiol 1956; 9:25-29.

95. Ashton CH, McHardy GJR. A rebreathing method for determining mixed venous PCO_2 during exercise. J Appl Physiol 1963; 18:668-671.

96. Spiro SG. Exercise testing in clinical medicine. Br J Dis Chest 1977; 71:145-172.

97. Wasserman K. The anaerobic threshold measurement to evaluate exercise performance. Am Rev Respir Dis 1984; 129(Suppl):S35-S40.

98. Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. Am J Cardiol 1964; 14:844-852.

99. Lowe GDO, Drummond MM, Lorimer AR, et al. Relation between extent of coronary artery disease and blood viscosity. Brit Med J 1980; i:673-674.

100. Clivati A, Marazzini L, Agosti R, Gatto R, Longhini E. Effect of hematocrit on the blood viscosity of patients with chronic respiratory failure and secondary polycythemia. Respiration 1980; 40:201-207.

101. Dinakara P, Blumenthal WS, Kauffman LA, Solnick PB. The effect of anemia on pulmonary diffusing capacity with derivation of a correction equation. Am Rev Respir Dis 1970; 102:965-969.

102. Herbert SJ, Weill H, Stuckey WJ, Urner C, Gonzales E, Ziskind MM. Pulmonary diffusing capacity in polycythemic states before and after phlebotomy. Chest 1965; 48:408-415.

103. Burgess JH, Bishop JM. Pulmonary diffusing capacity and its subdivisions in polycythemia vera. J Clin Invest 1963; 42:997-1006.

104. Greening AP, Patel K, Goolden AWG, Munro AJ, Hughes JMB. Carbon monoxide diffusing capacity in polycythaemia rubra vera. Thorax 1982; 37:528-531.

105. Clark EH, Woods RL, Hughes JMB. Effect of blood transfusion on the carbon monoxide transfer factor of the lung in man. Clin Sci Mol Med 1978; 54:627-631.

106. Roughton FJW, Forster RE. Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity and volume of blood in the lung capillaries. J Appl Physiol 1957; 11:290-302.

107. Murray JF, Gold P, Johnson BL. The circulatory effects of hematocrit variations in normovolaemic and hypervolaemic dogs. J Clin Invest 1963; 42:1150-1159.

108. Cotes JE, Dabbs JM, Elwood PC, Hall AM, McDonald A, Saunders MJ. Iron-deficiency anaemia: its effect on transfer factor for the lung (diffusing capacity) and ventilation and

cardiac frequency during sub-maximal exercise. Clin Sci 1972; 42:325-335.

109. Gledhill N. Blood doping and related issues: a brief review. Med Sci Sports Exerc 1982; 14:183-189.

110. Spriet LL, Gledhill N, Froese AB, Wilkes DL. Effect of graded erythrocythaemia on cardiovascular and metabolic responses to exercise. J Appl Physiol 1986; 61:1942-1948.

111. Ekblom B, Goldbarg AN, Gullbring B. Response to exercise after blood loss and reinfusion. J Appl Physiol 1972; 33:175-180.

112. Buick FJ, Gledhill N, Froese AB, Spriet LL, Meyers EC. Effect of induced erythrocythaemia on aerobic work capacity. J Appl Physiol 1980; 48:636-642.

113. Williams MH, Goodwin AR, Perkins R, Bocrie J. Effects of blood reinjection upon endurance capacity and heart rate. Med Sci Sports Exerc 1973; 5:181-186.

114. Williams MH, Lundhjem M, Schuster R. The effect of blood infusion upon endurance capacity and ratings of perceived exertion. Med Sci Sports Exerc 1978; 10:113-118.

115. Brodal P, Ingjer F, Hermansen L. Capillary supply of skeletal muscle fibres in untrained and endurance-trained men. Am J Physiol 1977; 232:H705-H712.

116. Daniel MK, Bennett B, Dawson AA, Rawles JM. Haemoglobin concentration and linear cardiac output, peripheral resistance, and oxygen transport. Brit Med J 1986; 292:923-926.

117. Clark TJH, Freedman S, Campbell EJM, et al . The ventilatory capacity of patients with chronic airways obstruction. Clin Sci 1969; 36:307-316.

118. Sannerstedt R. Hemodynamic response to exercise in patients with arterial hypertension. Acta Med Scand 1967; 180(Suppl 458):699-706.

119. Jones NL, Campbell EJM, Edwards RHT, Wilkoff WG. Alveolar-to-blood PCO_2 difference during rebreathing in exercise. J Appl Physiol 1969; 27:356-360.

120. McHardy GJR. Relationship between the difference in pressure and content in arterial and venous blood. Clin Sci 1967; 32:299-309.

Appendix 1: Predicted values in exercise testing

Maximum heart rate[96]: $HR = 210 - 0.65 \times age(yrs)$

Maximum ventilation[117]: $V_E = 35 \times FEV_1$ (L)

If $FEV_1 < 1.2$ L[96] : $V_E = 20 + (20 \times FEV_1)$ (L)

Systolic BP[118]: $BP_s = 120 + 0.8 \times workload(kp \cdot m \cdot min^{-1})$

Diastolic BP should not change more than ± 10 mmHg

Workload[92]: $VO_2(max) = 60 - 0.55 \times age(yrs)$ $[ml \cdot kg^{-1} \cdot min^{-1}]$ Men

$= 48 - 0.37 \times age(yrs)$ $[ml \cdot kg^{-1} \cdot min^{-1}]$ Women

$VO_2(max)$ = Above figure x lean body mass $[ml \cdot min^{-1}]$

Workload = $[VO_2(max) - 3.5 \times mass(kg)]/2$ $[kp \cdot m \cdot min^{-1}]$

Appendix 2: Exercise test calculations

Typical measurements made are:

Inspired minute ventilation (ATPS) by dry gas meter:	V_I
Mixed expired CO_2, O_2 fractions:	F_eCO_2, F_eO_2
Barometric pressure:	P_B
Relative humidity:	H_R
Ambient temperature:	T_A

By convention, lung volumes and ventilation are reported as volume (BTPS) - i.e. at 37°C, ambient pressure, fully saturated with water vapour. Gas exchange variables (CO_2 production and O_2 consumption) are reported as volume (STPD) - i.e. at 0°C, 760 mmHg, dry. Measurements are made at ATPS - atmospheric pressure and temperature, fully saturated with water vapour. Conversion factors to convert ATPS volumes to BTPS and STPD need to be applied. These can be read from tables or calculated from the following[90]:

$$SVP = 9.993 - 0.3952 \times T_A + 0.03775 \times T_A^2$$

$$BTPS = (P_B - SVP)/(P_B - 47) \times (310/(273 + T_A))$$

$$STPD = (P_B - SVP)/760 \times (273/(273 + T_A))$$

Ventilation measured by dry gas meter or pneumotachograph is usually inspired ventilation as this minimises condensation in the recording apparatus. The expired ventilation (V_E) is usually slightly different to V_I because of the respiratory exchange ratio (R). The conversion can be made by using the nitrogen

content of air, which is assumed to be constant (Haldane's correction)[92].

$F_iN_2 \times V_I = F_eN_2 \times V_E$

$F_iN_2 = 1 - F_iO_2 = 1 - 0.2093 = .7904$

$F_eN_2 = 1 - F_eO_2 - F_eCO_2$

$V_E = V_I \times (0.7904/(1 - F_eCO_2 - F_eO_2))$

During exercise the most common variables calculated are the oxygen consumption (VO_2) and carbon dioxide production (VCO_2).

Minute ventilation (BTPS) = V_E or V_I x BTPS factor

VCO_2 (STPD) = V_E (STPD) x F_eCO_2 x 1000 $ml \cdot min^{-1}$ (STPD)

VO_2 (STPD) = [V_I (STPD) x 0.2093 - V_E (STPD) x F_eO_2] x 1000 $ml \cdot min^{-1}$ (STPD)

$R = VCO_2 / VO_2$

End-tidal PCO_2 can be calculated from the end-tidal FCO_2 as follows:

$P_{ET}CO_2 = F_{ET}CO_2 \times (P_B - 47)$ mm Hg

[Use (P_B - 6.3) if working in kPa]

Cardiac output calculation

Cardiac output is measured using the Fick principle:

$Q_t = VCO_2 / (C_vCO_2 - C_aCO_2)$

The mixed venous-arterial CO_2 content difference ($C_{v-a}CO_2$) can be calculated using the equation for the CO_2 dissociation curve:

$$\ln(C_aCO_2) = 0.396 \times \ln(P_aCO_2) + 2.4$$

The mixed venous PCO_2 (P_vCO_2) is obtained by the equilibration rebreathing method[94,95]. This needs to be corrected for the "downstream" effect[119]

$$P_vCO_2 = P_{eq}CO_2 - (0.24 \times P_{eq}CO_2 - 11)$$

The calculation for ($C_{v-a}CO_2$) then simplifies to:

$$(C_{v-a}CO_2) = 11.02 \times (P_vCO_2^{0.396} - P_aCO_2^{0.396})$$

This value has to be corrected for changes in haemoglobin concentration[120]:

$$\text{Corrected } (C_{v-a}CO_2) = (C_{v-a}CO_2) - (15-[Hb]) \times 0.015 \times (P_vCO_2 - P_aCO_2)$$